

Occupational exposures in rare cancers: A critical review of the literature

B. Charbotel^{a,b,c,*,1}, B. Fervers^{d,a,e,1}, J.P. Droz^{d,a,e}

^a Université de Lyon, F-69003 Lyon, France

^b Université Lyon 1, UMRESTTE (Unité mixte IFSTTAR/UCBL), Domaine Rockefeller, 69373 Lyon, France

^c Hospices Civils de Lyon, Service des Maladies Professionnelles, Centre Hospitalier Lyon Sud, 69495 Pierre Bénite, France

^d Unité Cancer et Environnement, Centre Léon Bérard, 28 rue Laënnec, 69373 Lyon Cedex 08, France

^e Université Lyon 1, Faculté Lyon Est, F-69008 Lyon, France

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Contents

| | |
|---|-----|
| 1. Introduction | 101 |
| 2. Methods | 101 |
| 3. Results | 101 |
| 3.1. Head and neck cancers | 101 |
| 3.1.1. Epithelial tumors of the nasal cavity and sinuses* | 101 |
| 3.1.2. Epithelial tumors of the nasopharynx* | 101 |
| 3.1.3. Epithelial tumors of the major salivary glands** | 101 |
| 3.1.4. Epithelial tumors of the hypopharynx* | 101 |
| 3.1.5. Epithelial tumors of the larynx* | 119 |
| 3.1.6. Epithelial tumors of the oropharynx** | 122 |
| 3.1.7. Epithelial tumors of the oral** cavity and lip* | 122 |
| 3.2. Gastrointestinal cancers | 122 |
| 3.2.1. Squamous cell carcinoma and adenocarcinoma of the esophagus** | 122 |
| 3.2.2. Carcinoma of the small intestine** | 122 |
| 3.2.3. Epithelial tumors of the anal canal | 123 |
| 3.2.4. Hepatocellular carcinoma of the liver and intrahepatic bile tract (IBT)* | 123 |
| 3.2.5. Epithelial tumors of gallbladder and extrahepatic biliary tract (EBT)** | 123 |
| 3.3. Thoracic cancers | 123 |
| 3.3.1. Epithelial tumor of the trachea | 123 |
| 3.3.2. Large cell lung carcinoma* | 123 |
| 3.3.3. Bronchioloalveolar carcinoma of the lung | 123 |
| 3.3.4. Epithelial tumors of the thymus | 123 |
| 3.3.5. Mesothelioma* | 123 |
| 3.4. Reproductive cancers | 123 |
| 3.4.1. Mammary Paget's disease of the breast | 123 |
| 3.4.2. Epithelial tumors of the male breast** | 123 |
| 3.4.3. Epithelial tumors of the cervix uteri** | 123 |
| 3.4.4. Adenocarcinoma of the ovary* | 124 |
| 3.4.5. Epithelial tumors of the vulva and vagina | 124 |
| 3.5. Urogenital cancers | 124 |
| 3.5.1. Testicular cancer** | 124 |
| 3.5.2. Extragonadal germ cell tumors | 124 |

* Corresponding author at: Université Lyon 1, UMRESTTE (Unité mixte IFSTTAR/UCBL), Domaine Rockefeller, 69373 Lyon, France. Tel.: +33 4 78772827.
E-mail address: barbara.charbotel@univ-lyon1.fr (B. Charbotel).

¹ These authors contributed equally to this work.

| | | |
|---------|---|-----|
| 3.5.3. | Epithelial tumors of the penis | 124 |
| 3.5.4. | Squamous cell carcinoma of the kidney | 124 |
| 3.5.5. | Non-transitional cell carcinoma of the urinary bladder | 124 |
| 3.5.6. | Non-bladder urinary organs (renal pelvis, ureter, and urethra)* | 124 |
| 3.6. | Neuroectodermic and mesodermic tumors | 124 |
| 3.6.1. | Malignant melanoma of the mucosa | 124 |
| 3.6.2. | Epithelial tumors of the eye and adnexa* | 124 |
| 3.6.3. | Malignant melanoma of the uvea* | 124 |
| 3.6.4. | Soft-tissue sarcoma (STS)* | 124 |
| 3.6.5. | Bone sarcoma* | 124 |
| 3.6.6. | Glial tumors of the central nervous system** | 125 |
| 3.6.7. | Malignant meningioma** | 125 |
| 3.7. | Neuroendocrine tumors | 125 |
| 3.8. | Endocrine tumors | 125 |
| 3.8.1. | Carcinomas of the pituitary gland | 125 |
| 3.8.2. | Carcinomas of the thyroid gland** | 125 |
| 3.8.3. | Carcinomas of the parathyroid gland | 125 |
| 3.8.4. | Carcinomas of the adrenal gland | 125 |
| 3.9. | Lymphoid diseases | 125 |
| 3.9.1. | Hodgkin disease (HD)** | 125 |
| 3.9.2. | Acute lymphoblastic leukemia (ALL)* | 125 |
| 3.9.3. | Burkitt leukemia/lymphoma | 125 |
| 3.9.4. | Cutaneous T cell lymphoma/mycosis fungoides** | 125 |
| 3.9.5. | Other T cell lymphomas and NK cell neoplasms** | 125 |
| 3.9.6. | Diffuse large B-cell lymphoma (DLCL)* and follicular B lymphoma (FL)* | 125 |
| 3.9.7. | Hairy cell leukemia (HCL)** | 126 |
| 3.9.8. | Multiple myeloma (MM)* | 126 |
| 3.9.9. | Other non-Hodgkin, mature B cell lymphoma | 126 |
| 3.10. | Acute myeloid leukemia (AML)* | 126 |
| 3.11. | Myeloproliferative neoplasms | 126 |
| 3.11.1. | Chronic myeloid leukemia* | 126 |
| 3.11.2. | Other myeloproliferative and myelodysplastic neoplasms** | 126 |
| 3.12. | Histiocytic and dendritic cell neoplasms | 126 |
| 3.13. | Childhood cancer | 127 |
| 3.13.1. | Childhood leukemia (CL)* | 127 |
| 3.13.2. | Lymphoma* | 127 |
| 3.13.3. | Childhood brain tumors (CBT)* | 127 |
| 3.13.4. | Neuroblastoma** | 127 |
| 3.13.5. | Ewing sarcoma* | 127 |
| 3.13.6. | Wilms' tumor** | 127 |
| 3.13.7. | Other childhood cancer** | 127 |
| 4. | Discussion | 127 |
| | Conflict of interest statement | 129 |
| | Role of the funding source | 129 |
| | Reviewers | 129 |
| | References | 129 |
| | Biographies | 134 |

Abstract

The contribution of occupational exposures to rare cancers, which represent 22% of all cancers diagnosed annually in Europe, remains insufficiently considered. We conducted a comprehensive review of occupational risk factors in 67 rare cancers (annual incidence <6/100,000). An examination of relevant articles in PubMed (1960–2012) and the International Agency for Research on Cancer (IARC) monographs revealed that 26 cancer sites, such as mesothelioma, nasal, larynx, liver, ovarian cancer, bone sarcoma, and hematopoietic malignancies were consistently linked to occupational factors. Main exposures included asbestos, wood dust, metals/metalloids, formaldehyde, benzene, vinyl chloride, and radiation. There was inconsistent evidence regarding 22 rare malignancies. We did not identify relevant data for 19 rare cancers. Despite limitations of published evidence, our review provides useful information that can facilitate the identification of work-related factors that contribute to rare cancers. International collaborations, development of improved exposure assessment methods, and molecular approaches can improve future studies.

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Keywords: Rare cancer; Occupational; Exposure; Epidemiology; IARC; Classification

1. Introduction

Despite their low occurrence, more than 500,000 rare cancers are diagnosed each year in Europe, corresponding to 22% of all cancers annually and one quarter of the total cancer prevalence [1]. Several rare malignancies are now well known to be caused by occupational factors, such as pleural mesothelioma in asbestos workers [2,3], nasopharyngeal carcinoma in wood workers [4] or liver angiosarcoma in vinyl chloride workers [5]. However, occupational exposures in many rare cancers remain under-reported due to lack of evidence and/or awareness by clinicians. Therefore, our article aimed to review the available evidence from epidemiology studies and IARC monographs to provide a synthesis of established and suspected occupational exposures associated with rare cancers.

2. Methods

We only considered here rare cancers, i.e., those with an incidence of <6 per 100,000 cases per year, according to RARECARE [1]. We searched PubMed from 1960 to December 2012, using search terms related to occupational exposure and specific cancer sites (Table 1). We included articles in English, French, German or Spanish. Overall, we identified 6820 articles. Possibly relevant articles were selected through assessment of titles and abstracts and through the reference lists of related articles. We further searched the International Agency for Research on Cancer (IARC) monographs (<http://monographs.iarc.fr/>). Studies were selected according to the following criteria: study design (cohort or case–control study); original study or meta-analyses; studies providing histology to differentiate between subtypes; studies providing information on association between cancer risk (effect size) and occupational exposure (i.e., included odds ratio [OR], relative risk [RR], standardized incidence ratio [SIR], or mortality rate ratio [SMR]). We selected in priority studies with detailed occupational exposure assessment, rather than studies based solely on job titles. When available, we preferentially selected meta-analyses. Only associations supported by consistent evidence from several studies were recorded (Tables 2 and 3). Also, when an association was consistently supported by numerous studies, the most recent data were retained. Finally, 187 articles and relevant data from IARC monographs were included (Tables 2 and 3).

3. Results

We included 67 rare cancers in our review. For 26 cancers (marked with an asterisk (*)), an association with occupational exposure was supported by IARC monographs and/or consistent evidence from epidemiology studies (Tables 2 and 3). We distinguished for each cancer site,

occupational exposures classified by IARC with “*sufficient evidence*” for carcinogenicity (i.e. a causal relationship has been established between exposure to the agent and the given cancer type) or “*limited evidence*” for carcinogenicity (i.e. a positive association for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence) [6] as well as occupational exposures supported by consistent epidemiology evidence. For 22 rare malignancies (marked with two asterisks (**)), there was inconsistent or insufficient evidence (Table 3). Finally, we did not identify relevant occupational exposure studies for 19 cancers (Table 3). Some histology subtypes or rare cancers are covered by the IARC classification for a larger cancer entity. This is specified in the text and tables (Tables 2 and 3). Unless otherwise stated for a cancer site, no IARC classification exists.

3.1. Head and neck cancers

3.1.1. Epithelial tumors of the nasal cavity and sinuses*

IARC has classified several occupational exposures as carcinogens for nasal cavity and sinuses with sufficient evidence (isopropyl alcohol production, leather dust, nickel compounds, radium, wood dust) or limited evidence (carpentry and joinery, chromium (VI) compounds, formaldehyde, textile manufacturing). Epidemiological studies have consistently associated cancer of the nasal cavity with wood dust, leather dust, nickel and radium [4,7–10]. Epidemiological evidence remains insufficient for other agents including chromium, arsenic, formaldehyde and welding fumes [7,11–13]. Adenocarcinomas has been associated with wood dust, leather dust, and formaldehyde [7,13], whereas squamous cell carcinomas has been recently linked to arsenic and welding fumes [7].

3.1.2. Epithelial tumors of the nasopharynx*

IARC has classified wood dust and formaldehyde as carcinogenic for nasopharynx with sufficient evidence [14–17]. Also, nasopharyngeal carcinoma has been associated with chlorophenol exposure, mainly for machinists [18], as well as industrial heat [17].

3.1.3. Epithelial tumors of the major salivary glands**

Although few studies have focused on salivary gland cancer, occupational exposure to either ionizing radiation or formaldehyde have been linked to this cancer type [19].

3.1.4. Epithelial tumors of the hypopharynx*

Few studies have considered the hypopharynx separately from pharyngeal cancer. IARC has classified asbestos exposure as carcinogenic for pharynx with limited evidence. A twofold increase in hypopharyngeal cancer risk was identified for asbestos exposure [20]. Increased risk has also been reported for exposure to iron and steel [21].

Table 1

Search strategy and number of paper identified by cancer site.

| Cancer type | Search strategy | Number of references identified |
|--|---|---------------------------------|
| <i>Search terms related to occupational exposure:</i> | | |
| ((occupation[Tiab] OR occupational[Tiab] OR work[Tiab] OR worker*[Tiab]) AND (exposure[Tiab] OR exposures[Tiab] OR exposed[Tiab]) AND (English[lang] OR French[lang] OR German[lang] OR Spanish[lang])). | | |
| <i>Search terms related to specific cancer sites:</i> | | |
| Adapted from the National Cancer Institute: http://www.cancer.gov/cancertopics/litsearch | | |
| Head and neck cancers | | |
| Cancer of the nasal cavity and sinuses | (nose neoplasm*[Tiab] OR ((nose[Tiab] OR nasal[Tiab] OR sinonasal[Tiab] OR paranasal[Tiab] OR sinus[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]))) | 403 |
| Naso-pharyngeal cancer (NPC) | (nasopharynx[Tiab] OR nasopharyngeal[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]) | 87 |
| Cancers of the salivary gland | (salivary gland neoplasm*[Tiab]) OR ((salivary[Tiab] OR parotid[Tiab] OR sublingual[Tiab] OR submandibular[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 30 |
| Hypo-pharyngeal cancer | (hypopharyngeal neoplasms[Tiab]) OR ((hypopharynx*[Tiab] AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 17 |
| Laryngeal cancer | (laryngeal neoplasms[Tiab] OR ((laryngeal[Tiab] OR larynx[Tiab] OR glottis[Tiab] OR glottic[Tiab] OR subglottis[Tiab] OR subglottic[Tiab] OR supraglottis[Tiab] OR supraglottic[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]))) | 276 |
| Pharyngeal cancer | pharyngeal neoplasms[Tiab]) OR ((pharynx*[Tiab] AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 118 |
| Oropharyngeal cancer | oropharyngeal neoplasms[Tiab]) OR ((oropharynx*[Tiab] AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 25 |
| Cancer of the oral cavity | (oral[Tiab] OR mouth[Tiab] OR lip[Tiab] OR gingiva[Tiab] OR gingival[Tiab] OR tongue[Tiab] OR palate[Tiab] OR palatal[Tiab] OR buccal[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]) | 405 |
| Cancer of the lip | | |
| Gastrointestinal cancers | | |
| Squamous cell carcinoma of the esophagus | (squamous cell[Tiab] AND (oesophag*[Tiab] OR esophagi*[Tiab])) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]) | 8 |
| Adenocarcinoma of the esophagus | (adenocarcinoma*[Tiab] AND (esophag*[Tiab] OR oesophag*[Tiab])) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]) | 15 |
| Carcinoma of the small intestine | ((duodenal neoplasm*[Tiab] OR ileal neoplasm*[Tiab] OR jejunal neoplasm*[Tiab]) OR (((small[Tiab] AND (intestine*[Tiab] OR intestinal[Tiab] OR bowel*[Tiab]) OR (duodenal[Tiab] OR duodenum[Tiab] OR ileal[Tiab] OR ileum[Tiab] OR jejunal[Tiab] OR jejunum[Tiab])) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]))) | 51 |
| Cancer of the anal canal | ((anus neoplasms[Tiab]) OR ((anal[Tiab] OR anus[Tiab] OR perianal[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 7 |
| Hepatocellular carcinoma of the liver and intrahepatic bile tract (IBT) | ((liver neoplasm*[Tiab] OR cholangiocarcinoma[Tiab] OR hepatocellular carcinoma*[Tiab] OR hepatoblastoma*[Tiab] OR hepatoma*[Tiab]) OR ((liver*[Tiab] OR intrahepatic[Tiab] OR hepatic[Tiab] OR hepatocellular[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]))) | 853 |
| Angiosarcoma | ((liver[Tiab] OR hepatic[Tiab]) AND angiosarcoma[Tiab]) | 107 |
| Epithelial tumors of gallbladder and extrahepatic biliary tract (EBT) | gallbladder[Tiab] OR extrahepatic[Tiab] | 36 |
| Thoracic cancers | | |
| Epithelial tumor of the trachea | ((trachea[Tiab] OR tracheal[Tiab])) AND (((cancer*[Tiab] OR tumor*[Tiab]) OR tumor*[Tiab]) | 41 |
| Large cell lung carcinoma | ((large[Tiab] AND cell[Tiab]) AND lung[Tiab]) AND ((carcinoma*[Tiab] OR cancer*[Tiab]) | 60 |

Table 1 (Continued)

| Cancer type | Search strategy | Number of references identified |
|--|---|---------------------------------|
| Bronchiolo-alveolar lung carcinoma | ((bronchiolo-alveolar[Tiab]) AND lung[Tiab]) AND (carcinoma*[Tiab] OR cancer*[Tiab]) | 2 |
| Epithelial tumors of the thymus | AND (thymoma[Tiab] OR (thymus[Tiab] AND (cancer*[Tiab] OR carcinoma*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]))) | 34 |
| Mesothelioma | (mesothelioma*[Tiab]) | 1007 |
| Reproductive cancers | | |
| Mammary Paget's Disease | ((mammary[Tiab]) AND paget's[Tiab]) AND disease[Tiab]) | 0 |
| Epithelial tumors of the male breast | (male[Tiab] AND (breast neoplasms[Tiab] OR dcis[Tiab] OR lcis[Tiab] OR ((breast*[Tiab] OR mammary[Tiab] OR nipple*[Tiab]) AND ((cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]) OR in situ[Tiab]))) | 95 |
| Epithelial tumors of the cervix uteri | (cervix neoplasms[Tiab]) OR((cervix[Tiab] OR cervical[Tiab] OR exocervix[Tiab] OR exocervical[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 144 |
| Ovarian cancer | (ovarian neoplasm*[Tiab]) OR ((ovarian[Tiab] OR ovary[Tiab] OR ovaries[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 170 |
| Carcinoma of the vulva and vagina | ((vaginal neoplasm*[Tiab] OR vulvar neoplasm*[Tiab]) OR ((vagina [Tiab] OR vulva[Tiab] OR (bartholin[Tiab] AND gland[Tiab])) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]))) | 8 |
| Urogenital cancers | | |
| Testicular cancer | (testicular neoplasms[majr] AND human[mh] AND english[la]) OR ((testicular[Tiab] OR testis[Tiab] OR testicle*[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]) | 152 |
| Extragenital germ cell tumors | (neoplasms, germ cell and embryonal[MeSH Terms] OR (germcell[Tiab] OR germ cell[Tiab] OR dysgerminoma[Tiab] OR extragenital[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 296 |
| Penis carcinoma | (penile neoplasms[majr] AND human[mh]) [la] OR ((penile[Tiab] OR penis[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 5 |
| Squamous cell carcinoma of the kidney | squamous[Tiab] AND cell[Tiab] AND kidney AND (adenocarcinoma*[Tiab] OR carcinoma*[Tiab]) | 10 |
| Non-transitional cell carcinoma of the urinary bladder | ((bladder neoplasms[majr] OR (bladder[Tiab] AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) AND (non-transitional[Tiab] OR squamous[Tiab] OR adenocarcinoma*[Tiab] OR sub-type[Tiab] OR histology*[Tiab])) | 54 |
| Non-bladder urinary organs (renal pelvis, ureter, urethra) | ((urologic neoplasms[majr] AND Carcinoma, Transitional Cell[majr])) OR ((urologic[Tiab] OR urinary[Tiab] OR urothelial[Tiab] OR urethra*[Tiab] OR paraurethra*[Tiab] OR ureter[Tiab] OR (renal[Tiab] AND pelvis[Tiab])) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]) AND (TCC[Tiab] OR (transitional[Tiab] AND cell[Tiab]))) | 76 |
| Neuroectodermic and mesodermic tumors | | |
| Malignant melanoma of mucosa | (melanoma[Tiab]) AND mucosa[Tiab]) | 2 |
| Epithelial tumors of the eye and adnexa | ((cancer*[Tiab]) OR tumor*[Tiab]) OR tumor*[Tiab]) AND ((eye[Tiab]) OR adnexa[Tiab]) | 81 |
| Malignant melanoma of the uvea | (melanoma*[Tiab] AND eye[Tiab]) | 29 |
| Soft-tissue sarcoma | (soft-tissue sarcoma*[Tiab]) | 90 |
| Bone sarcoma | (bone[Tiab]) AND sarcoma*[Tiab] | 27 |
| Glial tumors of the central nervous system | Glioma*[Tiab] OR (glial*[Tiab] AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab])) | 113 |
| Malignant meningioma | Meningioma*[Tiab] AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab]) | 26 |
| Neuroendocrine tumors | Neuroendocrine[Tiab]) AND ((cancer*[Tiab] OR carcinoma*[Tiab] OR malignant OR malignant*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab])) | 9 |
| Endocrine tumors | | |
| Carcinoma of the pituitary gland | ((pituitary neoplasms[Tiab] OR (pituitary[Tiab] AND (tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab] OR malignant*[Tiab])) | 34 |

Table 1 (Continued)

| Cancer type | Search strategy | Number of references identified |
|---|---|---------------------------------|
| Carcinoma of the thyroid gland | thyroid neoplasm*[Tiab] OR (thyroid[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR malignan*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab]) | 196 |
| Carcinoma of the parathyroid gland | ((parathyroid neoplasms[Tiab] OR parathyroid AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignan*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab])) | 10 |
| Carcinoma of the adrenal gland | adrenal cortical carcinoma[Tiab] OR ((adrenocortical[Tiab] OR adrenal[Tiab]) AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab])) | 28 |
| Lymphoid diseases | | |
| Hodgkin disease | ((hodgkin disease[majr] AND human[mh]) OR (((hodgkin[Tiab] OR hodgkins[Tiab]) NOT (non-hodgkin[ti] OR non-hodgkins[ti])) AND (lymphoma[Tiab] OR lymphomas[Tiab] OR disease[Tiab]))) | 35 |
| Acute lymphoblastic leukemia | ((lymphoblastic leukemia, acute[majr] AND human[mh]) OR (acute lymphoblastic leukemia[tiab] OR acute lymphocytic leukemia[tiab])) | 63 |
| Burkitt lymphoma | ((b-cell lymphoma[majr] AND human[mh]) OR (Burkitt[Tiab] AND (lymphoma[Tiab] OR lymphomas[Tiab]))) | 22 |
| Cutaneous T cell lymphoma/mycosis fungoides | ((cutaneous t-cell lymphoma[majr] AND human[mh]) OR CTCL[Tiab] OR (mycosis[Tiab] AND fungoides[ti]) OR (cutaneous[Tiab] OR skin[Tiab]) AND t-cell[Tiab] AND (lymphoma[Tiab] OR lymphomas[Tiab]))) | 22 |
| Other T cell lymphoma and NK cell neoplasms | ((t-cell lymphoma[majr] AND human[mh]) OR ((t-cell[Tiab] OR (t[Tiab] AND lymphoblastic[Tiab]) OR NK-cell[Tiab] OR anaplastic large cell[Tiab] OR angioimmunoblastic[Tiab] OR sezary syndrome[Tiab] OR angiocentric[ti]) AND (lymphoma[Tiab] OR lymphomas[Tiab]))) | 53 |
| Diffuse large B-cell lymphoma (DLBCL) | ((b-cell lymphoma[majr] AND human[mh]) OR ((b-cell[Tiab] OR large-cell[Tiab] OR diffuse well-differentiated lymphocytic[Tiab] OR large-b-cell [Tiab]) AND (lymphoma[Tiab] OR lymphomas[Tiab]))) | 58 |
| Follicular B lymphoma (FL) | ((b-cell lymphoma[majr] AND human[mh]) OR (follicular[Tiab] AND (lymphoma[Tiab] OR lymphomas[Tiab]))) | 37 |
| Hair cell leukemia | ((hairy cell leukemia[majr] AND human[mh]) OR (hairy[Tiab] AND cell[Tiab] AND (leukemia[Tiab] OR leukemias[Tiab] OR leukemia[Tiab] OR leukaemias[Tiab])) OR ((leukemic[Tiab] OR leukaemic[Tiab])) | 87 |
| Multiple myeloma (MM) | ((plasmacytoma[majr] AND human[mh]) OR MGUS[Tiab] OR plasmacytoma[Tiab] OR plasmacytomas[Tiab] OR multiple myeloma[Tiab] OR multiple myelomas[Tiab] OR plasma cell neoplasm[Tiab] OR plasma cell neoplasms[Tiab]) | 205 |
| Other non-Hodgkin, mature B cell lymphoma | | |
| Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) | ((lymphocytic leukemia, chronic[majr] AND human[mh]) OR CLL[Tiab] OR mu heavy chain disease[Tiab] OR mu-chain disease[Tiab] OR ((chronic[Tiab] OR b-cell[Tiab]) AND (lymphocytic[Tiab] OR lymphoid[Tiab] OR lymphogenous[Tiab] OR aleukemic[Tiab] OR aleukaemic[Tiab]) AND ((leukemia[Tiab] OR leukemias[Tiab] OR leukemia[Tiab] OR leukaemias[Tiab]) OR disorders[Tiab]))) | 136 |
| Marginal zone lymphoma/MALT lymphoma | ((b-cell lymphoma[majr] AND human[mh]) OR ((MALT[Tiab] OR marginal zone[Tiab]) AND (lymphoma[Tiab] OR lymphomas[Tiab]))) | 18 |
| Mantle cell lymphoma | ((b-cell lymphoma[majr] AND human[mh]) OR (mantle cell[Tiab] AND (lymphoma[Tiab] OR lymphomas[Tiab]))) | 17 |
| Lymphoplasma-citic lymphoma/macroglobulinemia Waldstrom | ((b-cell lymphoma[majr] AND human[mh]) OR ((lymphoplasmacytic[Tiab] OR waldenstrom[Tiab] OR macroglobulinemia[Tiab]) AND (lymphoma[Tiab] OR lymphomas[Tiab]))) | 21 |
| Acute myeloid leukemia | ((myeloid leukemia, acute[majr] AND human[mh]) OR (AML[ti] OR acute myeloid leukemia[ti] OR acute myelogenous leukemia[ti] OR acute myeloblastic leukemia[ti])) | 167 |
| Chronic myeloid leukemia | ((myelogenous leukemia, chronic[majr] AND human[mh]) OR (CML[Tiab] OR (chronic[Tiab] AND (myeloid[Tiab] OR myelogenous[Tiab] OR granulocytic[Tiab]) AND (leukemia[Tiab] OR leukemias[Tiab] OR leukemia[Tiab] OR leukaemias[Tiab] OR disorders[Tiab]))) | 90 |
| Other myelodysplastic and myeloproliferative neoplasms | ((“myelodysplastic myeloproliferative diseases”[MeSH Major Topic] AND human[mh]) OR ((myelodysplastic [Tiab] OR myeloproliferative [Tiab]) AND (leukemia[Tiab] OR leukemias[Tiab] OR leukemia[Tiab] OR leukaemias[Tiab] OR disorders[Tiab]))) | 46 |
| Histiocytic and dendritic cell neoplasms | ((histiocytic[Tiab] OR dendritic[Tiab]) AND (neoplasm[Tiab] OR neoplasms[Tiab] OR sarcoma[Tiab] OR sarcomas[Tiab] OR lymphoma[Tiab] OR lymphomas[Tiab])) | 6 |
| Childhood cancer | parental[Tiab] OR maternal[Tiab] OR paternal[Tiab] OR childhood[Tiab] OR offspring[Tiab] OR prenatal[Tiab] AND (cancer*[Tiab] OR carcinoma*[Tiab] OR adenocarcinoma*[Tiab] OR malignan*[Tiab] OR tumor*[Tiab] OR tumor*[Tiab] OR neoplasm*[Tiab] OR leukemia[Tiab] OR lymphoma[Tiab]) | 500 |

Table 2

Associations supported by consistent evidence and relevant IARC classifications by cancer site.

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|--|-----------------------|---|---|
| Head and neck cancers | | | |
| Cancer of the nasal cavity and sinuses | Wood dust | d'Errico et al. [7] : Hospital based case control study (113 cases, 336 controls) OR for adenocarcinoma: 58.6 (23.74–144.8), adjusted for age and sex Demers et al. [4] : data from 12 case control studies (680 male cases, 2349 male controls, 250 female cases, and 787 female controls) Adenocarcinoma among men: OR = 3.1 (1.6–6.1) for moderate exposure and 45.5 (28.3–72.9) for high wood dust, adjusted for study and age Little evidence for squamous cell carcinoma | Group 1. Sufficient evidence for this specific site. (Vol. 100 C, 2012) |
| | Nickel | Grimsrud et al. [8] : Cohort study among workers employed at a nickel refinery (2 cases, 0.23 expected) SMR = 870 (105–3141) | Group 1. Sufficient evidence for this specific site. (Vol. 100 C, 2012) |
| | Leather dust | d'Errico et al. [7] : Hospital based case control study (113 cases, 336 controls) OR for adenocarcinoma: 26.6 (5.09–139.0) age and sex adjusted and 32.8 (5.96–181.1) when including wood dust exposure in the model | Group 1. Sufficient evidence for this specific site. (Vol. 100 C, 2012) |
| | Formaldehyde | d'Errico et al. [7] : Hospital based case control study (113 cases, 336 controls) OR for adenocarcinoma 9.5 (2.62–34.20) age and sex adjusted Luce et al. [13] : Pooled analysis of 12 studies (930 cases 3136 controls) from seven countries OR for adenocarcinoma in men: 3.0 (1.5–5.7) in the high level of exposure category, adjusted for age, exposure to wood dust and leather dust OR for adenocarcinoma in women 6.2 (2.0–19.7) in the high level of exposure category, adjusted for age | Group 1. Limited evidence for this specific site. (Vol. 100 F, 2012) |
| | Chromium | Rosenman et al. [11] : Cohort study among 3408 workers from facilities producing chromium compounds. 6 cases of sino-nasal cancers were observed. PMR = 6.85 (3.14–14.94) in white men. No adjustment. Hernberg et al. [12] : Case control study (167 cases and 167 controls) from Denmark, Finland or Sweden. OR = 2.7 (1.1–2.6). No adjustment. | Group 1. Limited evidence for this specific site. (Vol. 100 C, 2012) |
| | Arsenic | d'Errico et al. [7] : Hospital based case control study (113 cases, 336 controls) OR for squamous cell carcinoma: 5.2 (1.20–22.20) age and sex adjusted | Group 1. No evidence for this specific site. (Vol. 100 C, 2012) |
| | Welding fumes | d'Errico et al. [7] : OR for squamous cell carcinoma: 4.1 (1.66–10.13) age and sex adjusted | Group 2B. (Vol. 49, 1990) |
| Nasopharyngeal cancer (NPC) | Formaldehyde | Bachand et al. [14] : Meta-analysis on case control studies Overall OR = 1.22 (1.00–1.50), based on 6 case control studies Overall OR adjusted for smoking = 1.10 (0.8–1.51) based on 6 case control studies Bosetti et al. [15] : Meta-analysis on 12 cohort studies Meta-SMR = 1.33 (0.61–2.53) | Group 1. Sufficient evidence for this specific site. (Vol. 100 F, 2012) |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|------------------------------|--------------------------|--|--|
| | Wood dust | Hildesheim et al. [16]: OR for wood dust any level: 1.7 (1.0–3.0) adjusted for age, sex, education, and ethnicity >10 years OR = 2.4 (1.1–5.0); <i>p</i> for trend: 0.02; adjusted for age, sex, education, ethnicity Armstrong et al. [17]: case control study 282 cases with squamous cell nasopharyngeal carcinoma, 282 controls OR = 2.36 (1.33–4.19) adjusted for diet and cigarette smoke | Group 1. Sufficient evidence for this specific site. (Vol. 100 C, 2012) |
| | Chlorophenol | Mirabelli et al. [18]: 92 nasopharyngeal carcinoma cases from cancer registries and 1909 controls obtained through random digit dialing OR = 1.94 (1.03–3.50) among those with medium or high intensity chlorophenol exposure, adjusted for registry, age group, Asian ethnicity, and smoking status | Group 2B. (Vol. 71, 1999) |
| | Industrial heat | Armstrong et al. [17]: OR = 2.21 (1.12–4.33) adjusted for diet and cigarette smoke | No IARC classification for this exposure. |
| Cancer of the salivary gland | Ionizing radiations | Wilson et al. [19]: Death certificate-based case control study on salivary gland cancer. African American (168 cases, 672 controls) and white (2237 cases, 8748 controls) cases from 24 states (1984–1989) matched to controls by age, sex, race, and region. Job exposure matrix OR = 1.7 (1.05–2.80) in white men exposed to mid-high probability and intensity adjusted for age, marital and social status | Group 1. Sufficient evidence for this specific site but not from occupational exposure contexts. (Vol. 100 D, 2012) |
| | Formaldehyde | Wilson et al. [19]: OR = 1.6 (1.30–2.00) in white men exposed to mid-high probability and intensity adjusted for age, marital and social status | Group 1. No evidence for this specific site. (Vol. 100 F, 2012) |
| Hypo-pharyngeal cancer | Asbestos | Marchand et al. [20]: Hospital-based case control (206 hypopharyngeal cancer cases/305 controls with other types of cancer Ever exposed OR = 1.80 (1.08–2.99) adjusted for age, smoking, and alcohol consumption Highest level of exposure OR = 2.14 (1.14–4.01) adjusted for age, smoking, and alcohol consumption | Group 1. Limited evidence for pharynx. (Vol. 100 C, 2012) |
| | Mild steel dust | Shangina et al. [21]: Hospital controls based case control study (350 cases/34 hypopharyngeal cancer and 728) OR = 3.04 (1.39–6.64) adjusted for age, country, tobacco smoking, and alcohol consumption Dose–response relationship with cumulative exposure (<i>p</i> for trend 0.006) | Iron and steel founding (occupational exposure during) classified Group 1. No evidence for this site. (Vol. 100 F, 2012) |
| | Iron compounds and fumes | Shangina et al. [21]: OR = 2.74 (1.29–5.84) adjusted for age, country, tobacco smoking, and alcohol consumption Dose–response relationship with exposure duration (<i>p</i> for trend 0.03) | |
| Laryngeal cancer | Asbestos | Goodman et al. [24]: Meta-analysis based on 69 asbestos-exposed occupational cohorts Meta-SMR = 133 (114–155) IOM [25]: Meta-analysis of 15 cohort studies Any exposure overall relative risk: 1.4 (1.19–1.64) High exposure overall relative risk: 2.02 (1.64–2.47) | Group 1. Sufficient evidence for this specific site. (Vol. 100 C, 2012) |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|---------------------------|---|---|--|
| | Acid mists | Steenland [23] : Cohort of 1156 male steelworkers SIR = 2.2 (1.2–3.7) adjusted on tobacco smoking | Group 1. Sufficient evidence for this specific site. (Vol. 100 F, 2012) |
| | Silica dust | Chen et al. [26] : Meta-analysis <i>Case control studies</i> (n = 6): pooled OR = 1.39 (1.17–1.67) adjustment for smoking and alcohol consumption <i>Cohort studies silicosis cases</i> (n = 5): pooled SMR = 1.38 (0.79–1.96) <i>Silica dust exposed worker</i> : pooled SMR = 1.13 (0.82–1.45) based on six studies Pooled SIR = 1.50 (0.59–2.42) based on three studies | Group 1. No evidence for this specific site. (Vol. 100 C, 2012) |
| | Engine exhaust | Paget-Bally et al. [27] : Meta-analysis for agents with at least 10 available studies with homogenous exposure. 99 publications analyzed Meta-RR = 1.17 (1.05–1.30) | Engine exhaust, diesel Group 1. No evidence for this specific site. (Vol. 105, in prep, meeting in 2012) |
| | Polycyclic aromatic hydrocarbons (PAH) | Paget-Bally et al. [27] : Meta-analysis for agents with at least 10 available studies with homogenous exposure. 99 publications analyzed Meta-RR = 1.29 (1.10–1.52) | Some PAH-related exposures are Group 1 but none of them for this site of cancer. (Vol. 100 F, 2012) |
| | Chlorinated solvents | Shangina et al. [21] : Hospital based case control study (350 cases/316 laryngeal cancer cases and 728 controls) OR = 2.18 (1.03–4.61) adjusted for age, country, tobacco smoking, and alcohol consumption | No classification for this site. |
| | Passive smoking at work | Lee et al. [28] : Case control study 542 cases and 2197 controls who reported never using tobacco Duration of exposure > 15 years OR = 2.07 (1.04–4.11) adjusted for centers, age, sex, race/ethnicity, education, and alcohol drinking Duration of exposure > 15 years, never alcohol users OR = 5.45 (1.69–17.52) | Second-hand smoke Group 1. Limited evidence for this site. (Vol. 100 E, 2012) |
| | Ionizing radiation | Dupree et al. [29] : Retrospective cohort mortality study of 995 white males employed at a uranium processing facility (5 larynx cancer cases) SMR = 447 (144–1043) no adjustment | Group 1. No evidence for this specific site. (Vol. 100 D, 2012) |
| | Textile dust | Paget Bally et al. [27] : Meta-analysis for agents with at least 10 available studies with homogenous exposure (99 publications analyzed) Meta-RR = 1.41 (1.09–1.83) | Textile manufacturing industry (work in) is Group 2B. (Vol. 48, 1990) |
| | Electromagnetic field low-frequency (ELF) | Floderus et al. [30] : Swedish cohort study on 1,596,959 men and 806,278 women In men exposed to medium level (0.084–0.115 μ T) RR = 1.5 (1.2–1.9) adjusted for age In men exposed to high level ($\geq 0.116 \mu$ T) RR = 1.6 (1.3–2.0) adjusted for age | Group 2B. (Vol. 80, 2002) |
| | Sulfur mustard | Easton et al. [31] : Cohort of 2498 men and 1032 women employed in a manufacture of mustard gas SMR = 273, $p < 0.001$ (no adjustment) | Group 1. Limited evidence for this site. (Vol. 100 F, 2012) |
| Pharyngeal cancer | Welding fumes | Gustavsson et al. [32] : Community based case referent study (545 cases and 641 referents) More than 8 years of exposure: OR = 2.3 (1.1–4.7) accounting for age, region, alcohol consumption and tobacco smoking | Welding fumes classified group 2B. No classification for this site. (Vol. 49, 1990) |
| | Sulfur mustard | Easton et al. [31] : Cohort of 2498 men and 1032 women employed in a manufacture of mustard gas SMR = 549, $p < 0.001$ (no adjustment) | Group 1. No evidence for this site. (Vol. 100 F, 2012) |
| Cancer of the oral cavity | Wood dust | Smailyte et al. [33] : cohort of woodworkers exposed to softwood dust (1080 men and 438 women) Oral cavity SIR in males: 2.83 (1.29–5.37) | Group 1. No evidence for this site. (Vol. 100 C, 2012) |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|--|-------------------------------------|--|--|
| Cancer of the lip | Outdoor work | Kenborg et al. [35] : Nationwide, population-based case control study. 3187 male cases of lip cancer ascertained from the Danish Cancer Registry. 9361 controls Outdoor work >10 years, OR = 1.67 (1.38–2.03) adjusted for social class and place of birth | Solar radiations are Group 1. Limited evidence for this site. (Vol. 100 D, 2012) |
| Gastrointestinal cancers Squamous cell carcinoma of the esophagus | Carbon black | Parent et al. [36] : population based, case-control study (99 esophageal cancers/63 squamous cell esophageal carcinomas/1066 controls) Any exposure OR = 3.4 (1.5–7.7) adjusted for age, respondent status, birthplace, educational level, alcohol consumption, carotene index, smoking Substantial exposure OR = 8.9 (1.2–64.3) adjusted for age, respondent status, birthplace, educational level, alcohol consumption, carotene index, smoking | Group 2B. (Vol. 93, 2010) |
| | Sulfuric acid | Parent et al. [36] : Any exposure OR = 2.8 (1.2–6.1) adjusted for age, respondent status, birthplace, educational level, alcohol consumption, carotene index, smoking | Group 1. No evidence for this site. (Vol. 100 F, 2012) |
| | Chrysotile asbestos | Parent et al. [36] : Any exposure OR = 2.0 (1.1–3.8) adjusted for age, respondent status, birthplace, educational level, alcohol consumption, carotene index, smoking | Group 1. No evidence for this site. (Vol. 100 C, 2012) |
| | Polycyclic aromatic hydrocarbons | Gustavson et al. [32] : Community based case referent study (545 cases and 641 referents) Low level OR = 2.01 (1.16–3.48) adjusted for region, age, alcohol consumption and smoking habits High level OR = 1.87 (1.11–3.16) adjusted for region, age, alcohol consumption and smoking habits | Some compounds are Group 1. No evidence for this site. (Vol. 100 F, 2012) |
| Adeno-carcinoma of the esophagus | Sulfur compounds | Santibañez et al. [37] : Hospital-based case control study, 147 squamous cell carcinoma and 38 adenocarcinoma of esophagus and 285 frequency matched controls High level of exposure (0.025 ppm) OR for adenocarcinoma = 3.12 (1.00–9.77) adjusted for age, province, educational level, alcohol drinking and tobacco smoking | Group 1. No evidence for this site. (Vol. 100 F, 2012) |
| | Lead | Santibañez et al. [37] : High level of exposure High (.0237 mmol/l) OR for adenocarcinoma = 5.30 (1.39–20.22) adjusted for age, province, educational level, alcohol drinking and tobacco smoking | Group 2 B. (Vol. 23, Sup 7, 1987) |
| Cancer of the small intestine | Asbestos | Clin et al. [38] : Cohort of 2024 subjects occupationally exposed to asbestos (3 cases of small intestine cancer) SIR = 6.93 (1.39–20.25) among men with an exposure exceeding 80 fibers/mL × years (no adjustment) | Group 1. Limited evidence for colorectum. (Vol. 100 C, 2012) |
| | Semiautomatic arc welding (MIG/MAG) | Kaerlev et al. [39] : European case control study (79 cases, 579 colon cancer controls, and 2070 population controls) Small bowel adenocarcinoma OR = 5.0 (1.3–19.6) adjusted for country, year of birth, and sex | Welding fumes classified group 2B. No classification for this site. (Vol. 49, 1990) |
| | Organic solvents | Kaerlev et al. [40] : European case control study (84 cases and 2070 population controls) Small bowel carcinoid tumor OR = 2.0 (CI 1.0–4.2) adjusted for country, year of birth, and sex | No classification for this site. |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|---|----------------------------------|--|--|
| Hepatocellular carcinoma of the liver and intrahepatic bile tract (IBT) | Benzidine | Brown et al. [41] : Cohort of 997 individuals employed at a chemical production facility (4 cases of small intestine cancer) SIR = 18.4 (2.2–66.4) among workers with highest level of exposure (no adjustment) | Group 1. No classification for this site. (Vol. 100 F, 2012) |
| | Polychlorinated biphenyls (PCBs) | Ahrens et al. [45] : Case control study among men in six European countries (183 case, 1938 controls) Exposure to Oils with polychlorinated biphenyls OR = 2.8 (1.3–5.9) for carcinoma of the extrahepatic biliary tract (adjusted for age, country and gallstones) Prince et al. [46] : Cohort mortality study among 2572 workers highly exposed to polychlorinated biphenyls (PCBs) during the manufacture of electrical capacitors (11 deaths from biliary passage, liver and gall bladder cancer) SMR = 2.11 (1.05–3.77) (no adjustment) | Group 1. Limited evidence for this specific site. (Vol. 107, in prep, meeting in 2013) |
| | Vinyl chloride monomer | Mastrangelo et al. [47] : Case-referent study nested in a cohort of 1658 VCM workers Hepatocellular carcinoma OR = 1.71 (1.28–2.44) for each extra increase of 1000 ppm × years of VCM cumulative exposure (adjusted for alcohol and viral hepatitis infection) Boffetta et al. [48] : Meta-analysis (8 cohort studies). Two large studies considered liver cancers other than ASL separately ($n = 68$): Meta-SMR = 1.35 (1.04–1.77) (no adjustment) | Group 1. Sufficient evidence for this site of cancer. (Vol. 100 F, 2012) |
| | Toluene and xylene | Porru et al. [49] : Case control study (144 males with a liver cancer, 283 male controls) OR = 2.8 (1.0–7.6) for 20 or more years of exposure adjusted for age, residence, education, HBsAg and HCVAb positivity and heavy alcohol consumption | Toluene Group 3. Xylene Group 3. (Vol. 71, 1999) |
| | Trichloro-ethylene | Wartenberg et al. [50] : Review on trichloroethylene and cancer Liver cancer average risk: 1.9 (1.0–3.4) based on SIRs from 3 cohorts | Group 1. Limited evidence for this cancer site. (Vol. 106, in prep, meeting in 2012) |
| | Tetrachloro-ethylene | Lynge et al. [51] : Cohort of 10,600 laundry and dry-cleaning workers exposed to tetrachloroethylene and other solvents Liver cancer among women SIR = 3.4 (1.4–7.0) | Group 2A. No evidence for this site. (Vol. 106, in prep, meeting in 2012) |
| | Organic solvents | Chen et al. [52] : Meta-analysis of mortality among workers exposed to organic solvents from 55 studies Liver and biliary passages SMR = 119.7 (104.4–137.2) | |
| | Radon in underground miners | Darby et al. [53] : Collaborative analysis of 11 cohort studies Liver cancer SMR = 1.73 (1.29–2.28), no clear dose-exposure relation Tomasek et al. [54] : Cancer mortality in 4320 uranium miners in West Bohemia. 22 liver cancer cases. Liver O/E = 1.67 (1.04–2.52) | Group 1. No mention to this specific site. (Vol. 100 D, 2012) |
| | Plutonium | Sokolnikov et al. [55] : Cohort of 17,740 nuclear facility workers ERRs for liver cancer were 2.6 for males and 29 for females | Group 1. Sufficient evidence for liver. (Vol. 100 D, 2012) |
| | Magnetic field exposure (ELF) | Floderus et al. [30] : Swedish cohort study including 1,596,959 men from national census and job exposure matrix based on measurements. Biliary passage and liver Medium exposure (0.084–0.115 μ T) RR = 1.2 (1.1–1.4) age adjusted High exposure ($\geq 116 \mu$ T) RR = 1.3 (1.2–1.5) age adjusted | Group 2B. (Vol. 80, 2002) |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|---|----------------------------------|--|--|
| Hepatic angiosarcoma | Vinyl chloride monomer | Kielhorn et al. [5]: Review and Meta-Analysis (4 main cohort studies) The global SMR from European and north American studies for all liver cancer including angiosarcoma was 5.33 (4.23–6.82) reaching 280.0 among highest exposure group (no adjustment) | Group 1. Sufficient evidence for this site of cancer. (Vol. 100 F, 2012) |
| Epithelial tumors of gallbladder and extrahepatic biliary tract (EBT) | Radon in underground miners | Tomasek et al. [54]: Cancer mortality in 4320 uranium miners in West Bohemia. 12 EBT cases. Gallbladder and extrahepatic bile ducts O/E = 2.26 (1.16–3.94) | Group 1. No mention to this specific site. (Vol. 100 D, 2012) |
| Thoracic cancers | Asbestos | de Klerk et al. [57]: Cohort study among workers from Wittenoom asbestos industry (2400 men and 149 women, 71 lung cancer cases, 8 LCell) OR = 2.1 (1.0–4.3) (Ioge) cumulative exposure (fibers.ml.years) adjusted for tobacco smoking | Group 1. Sufficient evidence for lung cancer. (Vol. 100 C, 2012) |
| Large cell lung carcinoma | Diesel exhaust | Villeneuve et al. [58]: Case control study among men ≥ 40 years (1681 incident cases of lung cancer and 2053 population controls) OR across the three increasing tertiles of cumulative lifetime exposure: 1.06, 1.19, 1.68 ($p = 0.02$), adjusted for age, province, tobacco smoking, occupational exposure to silica and asbestos | Group 1. Sufficient evidence for lung. (Vol. 105, in prep, meeting in 2012) |
| Mesothelioma | Asbestos | Harding et al. [59]: Cohort of 98,912 asbestos workers (649 mesothelioma cases) SMR men: 13.3 (12.3–14.4) SMR women: 30.9 (18.3–48.8) Loomis et al. [60]: Cohort of 5770 asbestos textile workers (4 mesothelioma cases (not separately coded before 1999)) SMR = 10.92 (2.98–27.96) Berman et al. [2]: Meta-analysis from 11 cohort studies providing type of fibers SMR amphibole = 13.8 (3.5–26.3) | Group 1. Sufficient evidence for this site. (Vol. 100 C, 2012) |
| Reproductive cancers | Alkylphenolic compounds | Villeneuve et al. [64]: European case control study (104 cases and 1901 controls) OR = 3.8 (1.5–9.5) among subjects exposed above the median, adjusted for age, country, alcohol consumption, body mass index and education | Not classified. |
| Epithelial tumors of the male breast | Gasoline and combustion products | Hansen et al. [63]: Nationwide register based case control study on male breast cancer morbidity (230 cases and 12,880 control) OR = 2.5 (1.3–4.5) adjusted for birth year and socioeconomic status | Gasoline engine exhaust classified group 2B. (Vol. 105, in prep, meeting in 2012) |
| Epithelial tumors of the cervix uteri | Organic solvents | Weiderpass et al. [65]: Register linkage study in Finland among 413,877 female workers born (1906–1945), 1101 cervical cancer cases Aliphatic and alicyclic solvents RR = 1.3 (1.1–1.6) Aromatic-hydrocarbon solvents RR = 1.2 (1.1–1.4) Chlorinated-hydrocarbon solvents RR = 1.3 (1.0–1.7) | No classification for this site. |
| | Trichloroethylene | Wartenberg et al. [50]: Review on trichloroethylene and cancer (over 80 papers) SMR (from 4 mortality studies) average risk 1.7 (1.5–2.0) SIR (one cohort study) 2.4 (1.1–4.8) | Group 1. No evidence for this site. (Vol. 106, 2012) |
| | Metalworking fluids | Betenia et al. [66]: Cohort of 4374 female autoworkers followed from 1985–2004 SIR = 2.96 (2.11–4.02) based on 40 cases | No classification for this site. |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|--|--|---|--|
| Ovarian cancer | Asbestos | Camargo et al. [67] : Meta-Analysis including 18 studies SMR 1.77 (1.37–2.28) | Group 1. Sufficient evidence for this site. (Vol. 100 C, 2012) |
| | Silica dust | Wernli et al. [68] : Nested case control study 261 incident ovarian cancer cases and 3121 control women RR = 5.6 (1.4–23.6) among women exposed 10 years or more, adjusted for age and reproductive category | Group 1. No mention to this specific site. |
| | Diesel exhaust | Guo et al. [69] : Register-linkage study in Finland among female workers born 1906–1945 RR = 3.7 (1.4–9.9) among highest exposure group (≥ 10.0 mg/m ³ -years) adjusted for mean number of children, body mass index, socioeconomic status, age and calendar period; <i>p</i> for trend 0.006 | Group 1. No evidence for this specific site. (Vol. 105, in prep, meeting in 2012) |
| | Trichloroethylene | Morgan et al. [70] : Cohort of 20,508 aerospace workers (13 cases), 4733 with occupational exposure to trichloroethylene (8 cases) High cumulative exposure RR = 7.1 (2.1–23.5), no adjustment | Group 1. No evidence for this site. (Vol. 106, in prep, meeting in 2012) |
| Urogenital cancers | | | |
| Non-bladder urinary organs (renal pelvis, ureter, urethra) | Polycyclic aromatic hydrocarbons (PAH) | Jensen et al. [75] : Hospital-based case control study (96 cases (renal pelvis, ureter) 294 controls) Coke, coal OR = 4.0 (1.2–13.6); Asphalt, tar OR = 5.5 (1.6–19.6), adjusted for sex and lifetime tobacco consumption | Group 1. No classification for this site. Coal-tar pitch: limited evidence for bladder cancer, no classification for this site. (Vol. 100 F, 2012) |
| Neuroectodermic and mesodermic tumors | | | |
| Epithelial tumors of the eye and adnexa | Ultraviolet radiation | Vajdic et al. [76] : Population-based case control study in Australia (290 cases, 893 controls) Highest category of GSR-weighted (MJ/m ²) occupational outdoor hours during decade years OR = 2.1 (1.2–3.7) adjusted for age, region of birth, eye color, ability to tan and squinting as a child Håkansson et al. [77] : Cohort study on sunlight exposure and cancer incidence in the Swedish construction industry including 323,860 men (35 eye melanoma cases) Ocular melanoma in the highest exposed group RR = 3.4 (1.1–10.5) adjusted for age, smoking, and magnetic field exposure | UV-emitting tanning devices classified group 1 with sufficient evidence for this site. (Vol. 100 D, 2012) Welding classified Group 1 with sufficient evidence for eye. (Vol. 100 D, 2012) |
| Malignant melanoma of the uvea | | Guénel et al. [78] : French part of a European Case control study (50 cases, 479 controls) Ocular melanoma among men welders age adjusted OR = 7.3 (2.6–20.1) and dose-response relationship with job duration | |
| Soft-tissue sarcoma | PolyChloroPhenol | Hoppin et al. [79] : Population-based case control study among men (295 cases, 1908 controls) Odds ratios were adjusted for age, registry, race, medical radiations and exposure to herbicides High-intensity exposure OR = 1.79 (1.10–2.88). Duration-response trend (<i>p</i> for trend < 0.0001) 10 years of substantial exposure or more, OR = 7.78 (2.46–24.65) | Group 2B. Limited evidence for this site. (Vol. 71 and 100 F, 2012) |
| | 2,3,7,8-Tetrachloro-dibenzo-p-dioxin | Fingerhut et al. [80] : Cohort mortality study among 5172 workers at 12 plants in the United States that produced chemicals contaminated with TCDD SMR = 922 (190–2695) Collins et al. [81] : Cohort study of 1615 workers exposed to dioxins in trichlorophenol production SMR = 4.1 (1.1–10.5) | Group 1. Limited evidence for STS. (Vol. 100 F, 2012) |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|--|-----------------------|--|---|
| Bone sarcoma | Ionizing radiation | Carnes et al. [9] : cohort studies of 820 women working as radium watch-dial painters (46 bone sarcomas) Dose response relationships for bone sarcoma mortality: $p < 0.001$ | Group 1. Sufficient evidence for this site. (Vol. 100 D, 2012) |
| | Pesticides | Merletti et al. [83] : Multicenter case control study in 7 European countries. 96 bone sarcoma cases compared to 2632 controls OR adjusted for age, country, gender and number of job periods: 2.61 (1.49–4.57) | |
| Malignant meningioma | Lead (inorganic) | Rajaraman et al. [95] : Case control study of 197 meningioma cancers and 799 non-cancer controls In subject with ALAD2 variant allele and exposed to $100 \mu\text{g}/\text{m}^3\text{-year}$, OR = 12.8 (1.4–120.8) Navas-Acien et al. [96] : Historical cohort of all Swedish men and women RR = 2.36 (1.12–4.96) in male workers with possible exposure to lead (adjusted for age, Period, Geographical Category and Town Size and exposure to other chemicals) | Group 2 A. (Vol. 87, 2006) |
| Endocrine tumors Carcinoma of the thyroid gland | Ionizing radiations | Zielinski et al. [98] : Cohort study of the Canadian national dose registry of radiation workers SIR = 1.74 (1.40–2.10) Zabel et al. [100] : Among workers exposed more than 5 years prior to 1950: RR = 3.04 (1.01–10.78) | Group 1. Sufficient evidence for thyroid cancer in Atomic-bomb survivors, medical patients. (vol. 100 D, 2012) |
| | Organic solvents | Lope et al. [101] : Cohort of 2,992,166 Swedish workers employed in the 1970 census (2599 TC) Probable exposure to organic solvents among women, RR = 1.91 (1.05–3.45) after adjustment for exposure to ionizing radiations | |
| Lymphoid diseases Hodgkin disease | Pesticides | Karunanayake et al. [104] : Population-based, case control study (316 Hodgkin Lymphoma and 1506 controls). Adjustment for age, province of residence, medical and family history, use of other pesticides, correlated with chlorpyrifos use. Exposure to insecticide chlorpyrifos OR = 1.19 (1.03–1.37) All other pesticides showed not significant association or no association Orsi et al. [102] : Hospital based case control study (491 cases (87 HD); 456 controls); Analysis adjusted for age, socioeconomic category Fungicides OR 4.5 = (1.6–12.2); organochlorine OR = 4.7 (1.1–20.8) Organophosphate OR = 3.0 (1.0–9.4); Pyrethrin OR = 3.6 (1.2–11.2) Phenoline herbicide OR = 4.3 (1.1–17.2); Picoline OR = 9.4 (2.0–43.1) Amide OR 3.8 = (1.1–12.7); Urea herbicide OR = 10.8 (2.4–48.1) Khuder et al. [103] : Meta-analysis of 30 peer-reviewed studies. Occupational exposure as farmer: combined RR = 1.25 (1.11–1.42); 13 case–control studies: combined RR = 1.53 (1.18–1.98); 7 cohort studies combined RR = 1.08 (0.97–1.20); 10 mortality and morbidity studies: combined RR = 1.18 (1.02–1.36) | No classification for this site. |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|---------------------------------------|-------------------------|--|---|
| Acute lymphoblastic leukemia | Wood dust | Briggs et al. [105] : Population-based case control study (343 Hodgkin disease and 1910 controls) OR = 4.6 (1.6–13.3), adjusted for age and race | Group 1. No classification for this site. (Vol. 100 C, 2012) |
| | Benzene | Vlaanderen et al. [107] : MA of 44 studies (17 studies for ALL with 47 ALL cases). Meta-RR = 1.44 (95%CI 1.03–2.02) | Group 1. Limited evidence for ALL. (Vol. 100 F, 2012) |
| Diffuse large B-cell lymphoma (DLBCL) | Solvents | Cocco et al. [113] : Multicenter case-control study (2348 lymphoma cases (251 FL)/2462 controls). Adjustment for age, gender, education and center. All solvents: OR = 1.0 (0.8–1.2), <i>p</i> trend NS Wang et al. [117] : population-based case-control study in women (601 NHL cases (189 DLBCL)/717 controls). Adjustment for age, gender, education and center. Organic solvents, medium-high intensity OR = 2.1 (1.4–3.3), <i>p</i> trend < 0.01 Chlorinated solvents, medium-high intensity OR = 2.2 (1.4, 3.4), <i>p</i> trend < 0.01 Miligli et al. [120] : Population-based multicenter case-control study (1428 NHL (308 DLBCL)/1530 controls); adjustment for sex, age, education, and area Any solvent OR = 1.5 (1.0–2.1); Xylene OR = 2.3 (1.2–4.4); Toluene OR = 2.4 (1.3–4.6) | Limited evidence for Benzene Group 1. (Vol. 100 F, 2012) |
| | Trichloroethylene (TCE) | Purdue et al. [119] : population-based case-control study (1189 cases (293 follicular lymphoma, 366 DLBCL), 982 controls). Adjustment for age, sex, race, education level and area TCE > 150 ppm-hr/week OR = 1.11 (1.01–1.23), <i>p</i> trend = 0.03 TCE Cumulative exposure (estimated ppm-hr) > 112,320 OR = 1.07 (0.94–1.22), <i>p</i> trend NS Seidler et al. [115] : population-based case-control study (710 malignant lymphoma (158 DLBCL)/710 controls) adjustment for smoking (in pack years) and alcohol consumption TCE > 35 ppm*yr.: OR = 2.6 (0.7–3.0), <i>p</i> trend 0.03 | Group 1. Limited evidence for lymphoma. (Vol. 106, in prep, meeting in 2012) |
| | Ethylene oxide | Kiran et al. [136] : case-control study (2347 lymphoma cases (530 DLBCL) and 2463 controls), adjustment for age, sex, and participating center. Ever exposure to ethylene oxide OR = 1.3 (0.6–2.9) Exposed > 5% of working hours OR = 6.4 (1.8–23.0); <i>p</i> trend 0.063 | Group 1. Limited evidence for NHL. (Vol. 100 F, 2012) |
| Follicular B lymphoma (FL) | Solvents | Cocco et al. [113] : Multicenter case-control study (2348 lymphoma cases (251 FL)/2462 controls). Adjustment for age, gender, education and center. All solvents: OR = 1.3 (1.0–1.7), <i>p</i> trend < 0.001 Benzene, toluene and xylene combined: OR = 1.7 (1.2–2.5), <i>p</i> trend < 0.0001 Wang et al. [117] : population-based case-control study in women (601 NHL cases (136 FL)/717 controls) adjustment for age, family history of hematopoietic cancers, alcohol, and race Organic solvents, medium-high intensity OR = 1.3 (0.7–2.1), <i>p</i> trend NS Seidler et al. [115] : population-based case-control study (710 malignant lymphoma (92 FL)/710 controls) adjustment for smoking (in pack years) and alcohol consumption Chlorinated hydrocarbons > 47.3 ppm*yr.: OR = 3.9 (1.3–12.1), <i>p</i> trend = 0.04 | Limited evidence for Benzene Group 1. (Vol. 100 F, 2012) Xylenes: Group 3. Toluene: Group 3. Dichloromethane: Group 2B. 1,2-Dichloroethane Group 2B. (Vol. 71, 1999) |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|-----------------------|-------------------------|---|---|
| | Trichloroethylene (TCE) | Purdue et al. [119]: population-based case–control study (1189 cases (293 follicular lymphoma, 293 FL), 982 controls). Adjustment for age, sex, race, education level and area TCE > 150 ppm–hr/week OR = 3.7 (1.2–11.7), <i>p</i> trend = 0.005 TCE Cumulative exposure (estimated ppm–hr) > 112,320 OR = 1.17 (1.04–1.32), <i>p</i> trend = 0.01 | Group 1. Limited evidence for lymphoma. (Vol. 106, in prep, meeting in 2012) |
| Hair cell leukemia | Pesticides | Orsi et al. [102]: Hospital based case control study (491 cases (27 HCL); 456 controls); Analysis adjusted for age, socioeconomic category. Occupational exposure to organochlorine insecticides OR = 4.9 (1.1–21.2); Herbicides (Picoline OR = 4.1 (1.1–15.5), Triazine OR = 5.1 (1.4–19.3). Clavel et al. [122]: Hospital based case control study (226 HCL, 425 controls). Possible or definite occupational pesticides exposure OR = 1.5 (1.0–2.3). Definite organochlorines exposure OR = 2.1 (1.2–3.7); Definite organophosphorus exposure OR = 2.6 (1.1–57) Definite herbicide exposure OR = 2.0 (1.1–3.5); definite exposure to Triazine OR = 2.4 (1.2–4.8) Definite organic fungicides exposure OR = 2.9 (1.5–5.3); Duration of definite exposure to organic fungicides OR = 2.6 (0.9–7.5) and OR = 3.5 (1.4–8.3), for <10 years and >10 years of exposure respectively. After adjustment for smoking: OR = 7.5 (0.9–61.5) for exposure to organophosphorus insecticides, OR = 2.8 (1.4–5.6) for forage growing in non-smokers. Nordström et al. [123]: Population-based case-control study (121 male HCL; 484 controls) Exposure to herbicides OR = 2.9 (1.4–5.9), insecticides OR = 2.0 (1.1–3.5), fungicides OR = 3.8 (1.4–9.9), impregnating agents OR = 2.4 (1.3–4.6). After adjustment for age: herbicides OR = 1.8 (0.7–4.6), insecticides OR = 0.7 (0.3–3.7), fungicides OR = 2.1 (0.6–6.5), impregnating agents OR = 2.0 (1.0–3.9). | Group 2A: occupational exposures to non-arsenical insecticides (spraying and application) (Vol. 53, 1991) Several compounds classified 2B or 3 (Vol. 5 sup 7, 1987; Vol. 30, sup 7, 1987; Vol. 41, sup 7, 1987; Vol. 53, 1991) No classification for this site. |
| Multiple myeloma (MM) | Pesticides | Perrotta et al. [129]: Systematic review of 55 case control studies (1970–2007) Working as a farmer pooled OR = 1.39 (1.18–1.65) Working on a farm >10 years pooled OR = 1.87 (1.15–3.16) Ever occupational pesticides exposure OR = 1.47 (1.11–1.94) Herbicides exposure pooled OR = 2.19 (1.30–2.95) Pahwa et al. [130]: Population-based case control study (342 Multiple Myelomas and 1506 controls). Analysis adjusted for age, province of residence, medical and family history of MM, exposure to chemicals other than pesticides Carbamate insecticides OR = 1.81 (1.05–5.35) Fungicide captan OR = 2.35 (1.03–5.35) Orsi et al. [102]: Hospital based case control study (244 NHL (56 MM) and 456 controls); Analysis adjusted for age, socioeconomic category Occupational pesticides use OR = 3.5 (1.6–7.7); Insecticides OR = 2.8 (1.2–6.5); Fungicides OR = 3.2 (1.4–7.2); Herbicides OR = 2.9 (1.3–6.5) | |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|---|-----------------------|---|---|
| | Benzene | Lope et al. [128]: Historical cohort (1971–1989; 2992,166 workers; linkage with National Cancer and Death Registries). Multiple Myeloma 3127 men and 1282 women. Analysis adjusted for age, period and geographical area Male occupation in agriculture, forestry, and fishing RR = 1.18 (1.07–1.30) Male exposure to peaks of pesticides RR = 1.2 (1.07–1.34) | Group 2A: (occupational exposures to non-arsenical insecticides (spraying and application) (Vol. 53, 1991) |
| | | Pukkala et al. [73]: Historical cohort with record linkage in 5 Nordic countries (15 Million people; MM 22,106 men, 19,508 females) Male farmers SIR = 1.07 (1.03–1.11); female farmers SIR = 1.14 (1.05–1.24) | Several compounds classified B or 3 (Vol. 5, sup 7, 1987; Vol. 30, sup 7, 1987; Vol. 41, sup 7, 1987; Vol. 53, 1991) |
| | | Vlaanderen et al. [107]: Meta-analysis of 44 studies (26 studies corresponding to 284 MM) Meta-RR = 1.12 (0.98–1.27) | No classification for this site. |
| | | Infante et al. [125]: MA of 8 benzene cohorts (22 observed MM deaths) SMR = 1.61 (1.01–2.44); pooled weighted RR = 2.13 (1.31–3.46) | Group 1.Limited evidence for MM. (Vol. 100 F, 2012) |
| | | Sonoda et al. [127]: Meta-analysis (8 case-control studies) Meta OR = 0.74 (0.60–0.90) | |
| | Ethylene oxide | | Group 1. Limited evidence for MM. (Vol. 100 F, 2012) |
| | Engine exhaust | Sonoda et al. [127]: Meta-analysis (7 case-control studies) OR = 1.34 (1.14–1.57) | Diesel engine exhaust Group 1. Gasoline engine exhaust Group 2B. (Vol. 105, 2012) No classification for this site. |
| Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) | Benzene | Schnatter et al. [135]: pooled analysis of 3 cohort studies (370 cases (80 CLL); 1587 controls) OR = 1.49(0.81–2.75) | Group 1. Limited evidence for this site. (Vol. 100 F, 2012) |
| | Solvents | Vlaanderen et al. [107]: Meta-analysis of 44 studies (18 studies for CLL with 111 CLL cases) meta-RR 1.14 (0.78–1.67) Khalade et al. [134]: Meta-analysis of 15 (10 studies for CLL) Summary effect-size OR 1.31 (1.09–1.57) Cocco et al. [113]: Multicenter case-control study (2348 lymphoma cases (323 CLL)/2462 controls). Adjustment for age, gender, education and center; Bonferroni correction for multiple testing All solvents OR = 1.5 (1.1–1.9) <i>p</i> trend 0.000004; Benzene, Toluene and Xylene combined OR = 1.4 (1.0–1.9); <i>p</i> trend 0.000048 Purdue et al. [119]: population-based case-control study (1189 cases (141 CLL/SLL), 982 controls). Adjustment for age, sex, race, education level and area OR = 2.7 (1.2–5.8) <i>p</i> trend not significant. Seidler et al. [115]: population-based case-control study (710 malignant lymphoma 104 CLL/710 controls) adjustment for smoking (in pack years) and alcohol consumption, no positive association with solvents found Miligli et al. [120]: Population-based multicenter case-control study (1428 NHL 285 CLL and small lymphocytic lymphoma)/1530 controls); adjustment for sex, age, education, and area Dichloromethane OR = 3.2 (1.0–10.1); Toluene OR = 2.0 (1.0–4.0) | No IARC classification for this site. Xylenes: Group 3. Toluene: Group 3. Dichloromethane: Group 2B. (Vol. 71, 1999) |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|--|-----------------------|---|--|
| Marginal zone lymphoma/MALT lymphoma | Ethylene oxide | Kiran et al. [136] : case–control study (2347 lymphoma cases (406 CLL) and 2463 controls), adjustment for age, sex, and participating center. Ever exposure to ethylene oxide OR = 2.0 (0.8–4.7) Exposed >5% of working hours OR = 6.2 (1.3–29.3), <i>p</i> trend 0.028 | Group 1. Limited evidence for CLL. (Vol. 100 F, 2012) |
| | 1,3-Butadiene | Sielken et al. [138] : cohort study 16,585 workers (12,819 workers exposed). 81 leukemia mortalities, 71 among exposed workers. Slope per cumulative ppm-years, $\beta = 0.000417$, <i>p</i> = 0.000027 | Group 1. Sufficient evidence for haematolymphatic organs. No specific classification for this subtype. (Vol. 100 F, 2012) |
| | Solvents | Seidler et al. [115] : population-based case–control study (710 malignant lymphoma (38 marginal zone lymphoma)/710 controls) adjustment for smoking (in pack years) and alcohol consumption High occupational exposure to chlorinated hydrocarbons OR = 7.0 (1.8–26.3) | No IARC classification. |
| Acute myeloid leukemia | Benzene | Vlaanderen et al. [124] : Meta-analysis of (21 studies with 217 AML cases) Meta RR 1.68(1.35–2.10) Khalade et al. [134] : Meta-analysis of 15 studies (9 studies for AML) Summary effect-size 1.38 (1.15–1.64) | Group 1. Sufficient evidence for this site. (Vol 100F, 2012) |
| | Pesticides | Van Maele Fabry et al. [146] : Meta-analysis of 17 cohort and 16 case-control studies Meta RR = 1.55 (1.02–2.34) | Group 1: Arsenic (Vol. 100 C, 2012) Group 2A: Occupational exposures to non-arsenical insecticides (spraying and application) (Vol. 53, 1991) Captafol (Vol. 53, 1991) Several compounds classified 2B or 3 (Vol. 5, sup 7, 1987; Vol. 30, sup 7, 1987; Vol. 41, sup 7, 1987; Vol. 53, 1991) No classification for this site. |
| | Formaldehyde | Zhang et al. [132] : Meta-analyses of 21 studies (4 studies with myeloid leukemia subtype specific data) Meta RR for myeloid leukemia = 2.47 (1.42–4.27) | Group 1. Sufficient evidence for leukemia. No specific classification for this subtype. (Vol. 100 F, 2012) |
| | Radiation | Daniels et al. [145] : nested case-control study in nuclear worker cohort (369 leukemia deaths (150 AML) in 105,245 US nuclear workers) AML in the 6–14-years window (ERR per 100 mGy = 7.0 (0.079–32.0); adjusted for sex, race and hire year | Group 1. Sufficient evidence for leukemia. No specific classification for this subtype. (Vol. 100 D, 2012) |
| | | | |
| Chronic myeloid leukemia | Formaldehyde | Zhang et al. [132] : Meta-analyses of 21 studies (4 studies with myeloid leukemia subtype specific data) Meta RR for myeloid leukemia = 2.47 (1.42–4.27) | Group 1. Sufficient evidence for myeloid leukemia. (Vol. 100 F, 2012) |
| | Radiation | Daniels et al. [145] : nested case–control study in nuclear worker cohort (369 leukemia deaths (52 CML) in 105,245 US nuclear workers) CML (ERR per 100 mGy = 0.29 (<0 to 1.8); adjusted for sex, race and hire year | Group 1. Sufficient evidence for leukemia. (Vol. 100 D, 2012) |
| Other myelo-dysplastic and myelo-proliferative neoplasms | Benzene | Schnatter et al. [135] : pooled analysis of 3 cohort studies (370 cases (29 myelodysplastic syndromes (MDS) and 30 myeloproliferative disorders (MPD), 1587 controls) Cumulative exposure >2.93 ppm-years high and medium certainty diagnoses MDS OR = 4.33 (1.31–14.3); MPD OR = 1.79(0.68–4.74) | Group 1. No classification for this site. (Vol. 100F, 2012) |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|--------------------|---|---|---|
| Childhood leukemia | Parental occupational pesticides exposure | <p>Vinson et al. [164]: Meta-analysis of 40 studies: 3 cohort studies: OR = 0.95 (0.81–1.11); 37 case control studies: Paternal occupational exposure OR = 1.37 (1.23–1.52); Paternal exposure during prenatal period (occupation and environmental) OR = 1.32 (1.20–1.46); Maternal exposure during prenatal period (occupation and environmental) OR = 1.48 (1.26–1.75); Parental exposure to insecticides OR = 1.17 (1.03–1.33); Parental exposure to herbicides OR = 1.26 (1.14–1.39) Van Maele-Fabry et al. [162]: Meta-analysis of 25 studies: Maternal occupational exposure meta RR = 1.62 (1.22–2.16); Paternal occupational exposure meta RR = 1.14 (0.76–1.69) Wigle et al. [163]: Meta-analysis of 30 studies: Maternal occupational exposure (16 studies) OR = 2.09 (1.51–2.88) Paternal occupational exposure (30 studies) OR = 1.09 (0.88–1.34)</p> | <p>Group 1: Arsenic (Vol. 100 C, 2012) Group 2A: application of non-arsenical pesticides. Captafol (Vol. 53, 1991), Several compounds classified 2B or 3 (Vol. 5, sup 7, 1987; Vol. 30, sup 7, 1987; Vol. 41, sup 7, 1987; Vol. 53, 1991) No classification for this site.</p> |
| | Painting | <p>Schuz et al. [157]: Case control study (1138 ALL/2962 controls): Maternal pre-conceptional occupational exposure: OR = 1.6 (1.1–2.4) and during pregnancy: OR = 2.0 (1.2–3.3). Adjusted for socioeconomic status and degree of urbanization Shu et al. [155]: Case control study including 1842 ALL and 1986 controls. Maternal occupational exposure pre-conceptional OR = 1.6 (1.1–2.3) and during pregnancy OR = 1.7 (1.2–2.3). Adjusted for maternal education, race, and family income Buckley et al. [154]: Case control study with 204 AML/ANLL) Maternal exposure OR = 2.2 (0.9–5.4), prolonged spray paints exposure OR = 3.0 (trend, $p = 0.03$). Adjusted for other professional exposure Lowengart et al. [158]: registry based case control study (123 acute leukemia cases, 123 controls) paternal exposure after delivery to spray paint OR = 2.2 (0.96–4.39). No information on adjustment variables Van Steensel-Moll et al. [153]: Registry based case control study (519 ALL, 507 controls) Maternal occupational exposure during pregnancy RR = 2.4 (1.2–4.6)</p> | <p>Group 1. Limited evidence for this site. (Vol. 100 F, 2012)</p> |
| | Solvents | <p>Castro-Jimenez et al. [165]: Case control study (85 ALL and 85 individually matched neighborhood controls) Parental occupational exposure to hydrocarbons during 24 months before conception: mother only OR = 6.33 (1.41–28.31), both parents OR = 13.47 (3.31–54.71); adjustment for maternal age at child's birth, parental pre-conception smoking status, and maternal socioeconomic status during index pregnancy Infante-Rivard et al. [167]: Population-based case-control study (790 childhood ALL, 790 healthy controls) Maternal occupational exposure to solvents before and during pregnancy, adjusted for maternal age and sex. OR = 1.11 (0.88–1.40); mononuclear aromatic hydrocarbons OR = 1.64 (1.12–2.41)</p> | |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|--------------------|-----------------------|--|--|
| | | <p>Mc Kinney et al. [159]: Registry-based case control study (40,647 female workers, 47 childhood cancers); Childhood leukemia RR = 3.83 (1.17–12.55); all childhood malignancies RR = 2.26 (1.12–4.54) peri-conceptional maternal occupational exposure</p> <p>Schuz et al. [157]: Case control study (1138 ALL/2962 controls)</p> <p>Maternal occupational exposure pre-conceptional: OR = 1.2 (0.9–1.7) and during pregnancy: OR = 1.3 (0.8–1.9). Adjusted for socioeconomic status and degree of urbanization</p> <p>Smulevitch et al. [168]: Population-based case control study including 593 childhood cancers and 1181 controls Maternal occupational exposure OR = 3.1 (1.5–6.3) adjusted for parental alcohol consumption</p> <p>Shu et al. [155]: Case control study 1842 ALL and 1986 controls)</p> <p>Maternal occupational exposure pre-conception OR = 1.8 (1.3–2.5); during pregnancy OR = 1.6 (1.1–2.3) adjusted for maternal education, race, and family income</p> <p>Buckley et al. [154]: Case control study including 204 AML/ANLL</p> <p>Paternal exposure OR = 2.0 (1.2–3.8), adjusted for other professional exposures</p> <p>Lowengart et al. [158]: Registry based case control study (123 acute leukemia cases and 123 controls)</p> <p>Paternal exposure after delivery to chlorinated solvents OR = 3.5 (1.1–14.6). No information on adjustment variables</p> | <p>No IARC classification for this site.</p> <p>Xylenes: Group 3. Toluene: Group 3. Dichloromethane: Group 2B. 1,2-Dicloroéthane Group 2B. (Vol. 71, 1999)</p> |
| | Wood work | <p>Feychting et al. [160]: Birth cohort (235,635 children, 161 leukemias), registry linkage study</p> <p>Paternal pre-conceptional occupation in wood work RR = 2.18 (1.26–3.78). Adjusted for maternal age, socio-economic status, census year and gender</p> | <p>Group 1. No IARC classification for this site. (Vol. 100 C, 2012)</p> |
| Childhood lymphoma | Pesticides | <p>Vinson et al. [164]: Meta-analysis of 40 studies</p> <p>Paternal prenatal exposure (9 studies) OR = 1.37 (1.16–1.61)</p> <p>Maternal prenatal pesticides exposure (5 studies) OR = 1.53 (1.22–1.91)</p> <p>Ever exposure mother (6 studies) OR = 1.90 (1.14–3.17)</p> <p>Parental exposure to insecticides (11 studies) OR = 1.46 (1.20–1.78)</p> <p>Parental exposure to herbicides (4 studies) OR = 1.31 (1.02–1.67)</p> <p>Parental exposure to fungicides (3 studies) OR = 1.45 (1.06–1.99)</p> | <p>No IARC classification for this site.</p> |
| Ewing sarcoma | Pesticides | <p>Vinson et al. [164]: Meta-analysis</p> <p>Paternal occupational exposure (3 case control studies) OR = 2.34 (1.33–4.12); Maternal occupational exposure non-significant increased risk</p> <p>Valery et al. [186]: Meta-analysis of 5 case control studies with 199 cases and 1451 controls</p> <p>Paternal farm work OR = 2.3 (1.3–4.1) and maternal farm work OR = 3.9 (1.6–9.9) during pre-conception and gestation period</p> <p>After adjustment for farm residency OR = 1.4 (0.3–6.2) and OR = 1.7 (0.7–4.0) respectively</p> | <p>No IARC classification for this site.</p> |

Table 2 (Continued)

| Cancer type | Occupational exposure | Risk level (95% confidence intervals) | IARC Classification |
|-----------------------|--|--|--|
| Childhood brain tumor | Pesticides | Vinson et al. [164]: Meta-analysis of 40 studies Paternal occupational exposure (11 case control studies) OR = 1.40 (1.20–1.62); Maternal occupational exposure non-significant Paternal prenatal exposure (9 studies/OR) OR = 1.49 (1.23–1.79); Maternal prenatal exposure non-significant Parental exposure to herbicides (16 studies/OR) OR = 1.31 (1.08–1.60) Parental exposure to insecticides (24 studies/OR) OR = 1.18 (1.06–1.33) Parental exposure to fungicides (15 studies/OR) OR = 1.32 (1.06–1.65) Kristensen et al. [175]: Registry based cohort study including 323,292 children and 1275 cancer Parents farm holders, risk adjusted for year of birth and calendar year Risk of brain tumors ($n = 41$) RR = 1.71 (1.11–2.63) Risk of non-astrocytic neuroepithelial tumors ($n = 22$) RR = 3.37 (1.63–6.94) Feychting et al. [160]: Registry linkage study (235 635 children, 162 nervous system tumors) paternal pre-conceptional occupational exposure to pesticides RR = 2.36 (1.27–4.39), adjusted for maternal age, socio-economic status, census year and gender | No IARC classification for this site. |
| | Painting | Feychting et al. [160]: Registry linkage study (235 635 children, 162 nervous system tumors) paternal pre-conceptional work as painter RR = 3.65 (1.71–7.80) Adjusted for maternal age, socio-economic status, census year and gender | Group 1. No classification for this site. |
| | Polycyclic aromatic hydrocarbons (PAH) | Cordier et al. [179]: Case control study including 1218 cases and 2223 controls; adjusted for maternal age, sex of child, mother's level of education Paternal pre-conceptional occupational exposure to PAH All childhood brain tumors OR = 1.3 (1.1–1.6) Astroglial tumors OR = 1.4 (1.1–1.7) Astroglial tumors after exclusion of smoking fathers OR = 1.7 (1.3–2.3) Maternal occupational exposure OR = 1.11 (0.88–1.40) Johnson et al. [178]: Case control study with 499 childhood death from intracranial or spinal cord tumors and 998 controls Parental occupation with high PAH exposure: printers and graphics arts workers OR = 4.5 (1.4–14.7); chemical and petroleum workers levels: OR = 3.0 (1.1–8.5) | Some PAH-related exposures are Group 1 but none of them for this site of cancer. (Vol. 100 F, 2012) |
| | Diesel exhaust | Peters et al. [180]: Case control study including 306 cases and 950 controls Maternal exposure before child's birth OR = 2.03 (1.09–3.81) and paternal exposure around the time of the child's conception OR = 1.62 (1.12–2.34) | Group 1. No classification for this site. (Vol. 105, in prep, meeting in 2012) |
| Neuro-blastoma | Parental exposure to pesticides | Vinson et al. [164]: Meta-analysis OR = 1.70 (1.14–2.51) | No IARC classification for this site. |

3.1.5. Epithelial tumors of the larynx*

IARC has classified asbestos and acid mists as carcinogenic for larynx (sufficient evidence) as well as the rubber industry (limited evidence) [10,22,23]. The association with asbestos is supported by numerous studies and a meta-analysis [24,25]. Furthermore, meta-analyses have been conducted for several other occupational risks. Thus, Chen et al. reported evidence for an association with silica

dust, although only the pooled risk from case-control studies was statistically significant [26]. Moreover, Paget-Bailly et al. identified significant increased meta-relative risks associated with polycyclic aromatic hydrocarbons, engine exhaust, and textile dust [27]. A relationship with wood dust exposure has also been suggested, but a meta-analysis did not confirm this finding [27]. Similarly, although laryngeal cancer was suggested to be linked to chlorinated solvent exposure, this could

Table 3

Summary of the available evidence by cancer site.

| Cancer type | Occupational exposure (Group 1 carcinogen) with sufficient evidence supported by IARC classification | Occupational exposure with limited evidence supported by IARC classification or evidence from meta-analysis (^a) | Comments |
|---|--|--|--|
| Head and neck cancers | | | |
| Cancer of the nasal cavity and sinuses | Wood dust, Nickel, Leather dust, Isopropyl alcohol production, radium | Formaldehyde, Chromium, carpentry and joinery, textile manufacturing | |
| Naso-pharyngeal cancer (NPC) | Formaldehyde, Wood Dust | | Insufficient evidence ^c |
| Cancers of the salivary gland | | | |
| Hypo-pharyngeal cancer | | Asbestos | |
| Laryngeal cancer | Asbestos, Acid mists | Rubber industry Passive smoking at work, Sulfur mustard, Engine exhaust ^a , Silica dust ^a , Polycyclic aromatic hydrocarbons ^a , Textile dust ^a | |
| Pharyngeal/Oropharyngeal cancer | | | Insufficient evidence |
| Cancer of the oral cavity | | | Insufficient evidence |
| Cancer of the lip | | Outdoor work (solar radiations) | |
| Gastrointestinal cancers | | | |
| Squamous cell carcinoma of the esophagus | | | Insufficient evidence; Covered by the IARC classification for esophagus cancer ^b |
| Adenocarcinoma of the esophagus | | | Insufficient evidence; Covered by the IARC classification for esophagus cancer ^b |
| Carcinoma of the small intestine | | | Insufficient evidence |
| Cancer of the anal canal | | | No relevant data identified |
| Hepatocellular carcinoma of the liver and intrahepatic bile tract (IBT) | Vinyl chloride monomer, Plutonium, Thorium, Aflatoxin, Hepatitis B, Hepatitis C | Polychlorinated biphenyls, Trichloroethylene, Arsenic | |
| Hepatic angiosarcoma* | Vinyl chloride monomer | Radon in underground miners ^a | |
| Epithelial tumors of gallbladder and extrahepatic biliary tract (EBT) | | | Insufficient evidence |
| Thoracic cancers | | | |
| Epithelial tumor of the trachea | | | No relevant data identified |
| Large cell lung carcinoma | Asbestos, Diesel exhaust | | Covered by the IARC classification for lung cancer ^b |
| Bronchiolo-alveolar lung carcinoma | | | No relevant data identified |
| Epithelial tumors of the thymus | | | No relevant data identified |
| Mesothelioma | Asbestos, Erionite, Painting | | |
| Reproductive cancers | | | |
| Mammary Paget's Disease | | | No relevant data identified |
| Epithelial tumors of the male breast | | | Insufficient evidence; Covered by the IARC classification for breast cancer ^b |
| Epithelial tumors of the cervix uteri | | | Insufficient evidence |
| Ovarian cancer | Asbestos | | |
| Tumors of the vulva and vagina | | | No relevant data identified |

Table 3 (Continued)

| Cancer type | Occupational exposure (Group 1 carcinogen) with sufficient evidence supported by IARC classification | Occupational exposure with limited evidence supported by IARC classification or evidence from meta-analysis ^(a) | Comments |
|---|--|--|--|
| Urogenital cancers | | | |
| Testicular cancer | | | Insufficient evidence |
| Extragenital germ cell tumors | | | No relevant data identified |
| Penis carcinoma | | | No relevant data identified |
| Squamous cell carcinoma of the kidney | | | No relevant data identified; Covered by the IARC classification for kidney cancer ^b |
| Non-transitional cell carcinoma of the urinary bladder | | | No relevant data identified; Covered by the IARC classification for bladder cancer ^b |
| Non-bladder urinary organs (renal pelvis, ureter, urethra) | Aristolochloric acid | PAH | Transitional cell carcinoma of non-bladder urinary organs are covered by IARC classification for bladder cancer ^b |
| Neuroectodermic and mesodermic tumors | | | |
| Malignant melanoma of mucosa | | | No relevant data identified |
| Epithelial tumors of the eye and adnexa | Welding | Solar radiation | |
| Malignant melanoma of uvea | Welding | Solar radiation | |
| Soft-tissue sarcoma | | Polychlorophenol, 2,3,7,8-tetrachloro-dibenzo-p-dioxin | |
| Bone sarcoma | Ionizing radiation | | Insufficient evidence |
| Glial tumors of the central nervous system | | | Insufficient evidence |
| Malignant meningioma | | | No relevant data identified |
| Neuroendocrine tumors | | | |
| Endocrine tumors | | | |
| Carcinoma of the pituitary gland | | | No relevant data identified |
| Carcinoma of the thyroid gland | | | Insufficient evidence |
| Carcinoma of the parathyroid gland | | | No relevant data identified |
| Carcinoma of the adrenal gland | | | No relevant data identified |
| Lymphoid diseases | | | |
| Hodgkin disease | | | Insufficient evidence |
| Acute lymphoblastic leukemia | | Benzene | |
| Burkitt lymphoma | | | No relevant data identified; Insufficient evidence |
| Cutaneous T cell lymphoma/mycosis fungoides | | | |
| Other T cell lymphoma and NK cell neoplasms | | | Insufficient evidence; Covered by the IARC classification for lymphoma ^b |
| Diffuse large B-cell lymphoma (DLBCL) | | Benzene, Trichloroethylene | Covered by the IARC classification for lymphoma ^b |
| Follicular B lymphoma (FL) | | Benzene, Trichloroethylene | Covered by the IARC classification for lymphoma ^b |
| Hair cell leukemia | | | Insufficient evidence; Covered by the IARC classification for lymphoma ^b |
| Multiple myeloma (MM) | | Benzene, Ethylene oxide Pesticides ^a | |
| Other non-Hodgkin, mature B cell lymphoma | | | |
| Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) | | Benzene, Ethylene oxide | Insufficient evidence for SLL |

Table 3 (Continued)

| Cancer type | Occupational exposure (Group 1 carcinogen) with sufficient evidence supported by IARC classification | Occupational exposure with limited evidence supported by IARC classification or evidence from meta-analysis (^a) | Comments |
|---|--|--|---|
| Marginal zone lymphoma/MALT lymphoma | | | Insufficient evidence; Covered by the IARC classification for lymphoma ^b |
| Mantle cell lymphoma | | | No relevant data identified; Covered by the IARC classification for lymphoma ^b |
| Lymphoplasma-cytic lymphoma/macroglobulinemia Waldstrom | | | No relevant data identified |
| Acute myeloid leukemia | Benzene, Formaldehyde | | |
| Chronic myeloid leukemia | Formaldehyde, Radiation | | |
| Other myelodysplastic and myeloproliferative neoplasms | | | Insufficient evidence |
| Histiocytic and dendritic cell neoplasms | | | No relevant data identified |
| Childhood cancer | | | |
| Childhood leukemia | | Parental exposure to paintings Parental pesticides exposure ^a | |
| Childhood lymphoma | | Parental pesticides exposure ^a | |
| Childhood brain tumor | | Parental pesticides exposure ^a | |
| Neuroblastoma | | | Insufficient evidence |
| Ewing sarcoma | | Parental pesticides exposure ^a | |
| Wilms' tumor | | | Insufficient evidence |
| Other childhood cancer | | | Insufficient evidence |

^a Supported by meta-analyses.

^b <http://monographs.iarc.fr/ENG/Classification/index.php> (accessed October 2013).

^c Insufficient evidence for association with occupational exposure.

not be verified in a review of the literature [21,27]. Machining fluids have also been associated with laryngeal cancer, but results are inconsistent [27]. Finally, several carcinogens that are known to affect other sites have been reported to increase the risk of laryngeal cancer, including second hand smoke and ionizing radiation [28,29], whereas other suggested occupational factors might be seen as more anecdotal (e.g., extremely low frequency magnetic fields) [30].

3.1.6. Epithelial tumors of the oropharynx**

Few studies have focused on oropharyngeal cancers separately. When considering pharyngeal cancers, some occupational factors have been identified in the literature (i.e., sulfur mustard [31] and welding fumes [32]).

3.1.7. Epithelial tumors of the oral** cavity and lip*

IARC classified solar radiations as carcinogenic for lip (limited evidence). Wood dust has been suggested as a risk factor for cancer of the oral cavity [33]. Additionally, there is an increased risk of lip cancer associated with outdoor occupations (e.g., construction workers, seafarers, farmers) [34] and outdoor occupational activities [35].

3.2. Gastrointestinal cancers

3.2.1. Squamous cell carcinoma and adenocarcinoma of the esophagus**

IARC classified dry cleaning and rubber industry production as carcinogenic for esophagus (no distinction of histology subtype) with limited evidence [10].

For squamous cell carcinoma, associations with several agents have been suggested, including carbon black, sulfuric acid, asbestos, and polycyclic aromatic hydrocarbons (PAHs) [32,36]. On the other hand, adenocarcinoma has been linked to sulfur compounds and lead [37].

3.2.2. Carcinoma of the small intestine**

IARC has classified asbestos as carcinogenic for colon and rectum with limited evidence [10]. Nevertheless, a cohort study found a significant increase in the risk of small intestine cancer among men highly exposed to asbestos [38]. Additionally, an increased risk of small bowel adenocarcinoma has been found among workers exposed to semiautomatic arc welding [39]. However, no significant association was observed with other categories of welding or with welding activity in general. An elevated risk of small bowel carcinoma tumors was also reported for organic solvent-exposed

workers [40]. More recently, an increased risk for cancer of the small intestine has been suggested among workers exposed to benzidine [41].

3.2.3. Epithelial tumors of the anal canal

No relevant data identified.

3.2.4. Hepatocellular carcinoma of the liver and intrahepatic bile tract (IBT)*

IARC has classified several occupational exposures as carcinogens for liver and bile duct with sufficient evidence (aflatoxin, hepatitis B and C, plutonium, thorium-232 and its decay products, vinyl chloride) or limited evidence (arsenic, polychlorinated biphenyls, and trichloroethylene).

Aflatoxin is known to induce liver cancer, mainly via food contamination. However, workplace exposure to aflatoxin was also suggested to increase the risk of liver cancer in workers in the animal-feed processing industry [42] and other occupations [43,44].

Several other occupational exposures have been linked to liver cancer, in particular vinyl chloride monomer, organic solvents and polychlorinated biphenyls [45–52]. In fact, vinyl chloride monomer has been known to induce hepatic angiosarcoma for decades, and epidemiological studies have identified the association of this type of exposure with hepatocellular carcinoma [48]. An increased risk of liver cancer has been observed in workers exposed to radon [53,54] as well as in plutonium workers [55]. Magnetic fields were also associated with cancer at this site [30].

3.2.4.1. Hepatic angiosarcoma*. IARC has concluded that there is a causal relationship between hepatic angiosarcoma and vinyl chloride exposure (sufficient evidence). The strong association is supported by a positive dose–response relationship [5,56].

3.2.5. Epithelial tumors of gallbladder and extrahepatic biliary tract (EBT)**

IARC has classified thorium-232 and its decay products as carcinogenic for this site with sufficient evidence. Radon exposure has been reported to increase the risk of gallbladder, and extra hepatic bile ducts [54].

3.3. Thoracic cancers

3.3.1. Epithelial tumor of the trachea

No relevant data identified.

3.3.2. Large cell lung carcinoma*

IARC has classified numerous occupational exposures as carcinogens for lung with sufficient evidence (aluminum production, arsenic and inorganic arsenic compounds, asbestos, beryllium and compounds, bis(chloromethyl)ether; chloromethyl, methyl ether, cadmium and compounds, chromium(VI) compounds, coal, coal gasification, coal-tar

pitch, coke production, diesel engine exhaust, hematite mining, iron and steel founding, nickel compounds, painting, plutonium, radon-222 and its decay products, rubber production industry, crystalline silica dust, soot, sulfur mustard, secondhand tobacco smoke, X-radiation, gamma-radiation) or limited evidence (strong inorganic acid mists, manufacture of glass, bitumens, exposure to oxidized and hard bitumens, carbon electrode manufacture, alpha-chlorinated toluenes and benzoyl chloride, cobalt metal with tungsten carbide, creosotes, occupational exposures in spraying and application of insecticides, printing processes, 2,3,7,8-tetrachlorodibenzopara-dioxin, welding fumes) [10].

Few reports have distinguished cases based on histological subtype, and only two studies on large cell lung carcinoma were identified, which showed association with two common lung carcinogens: asbestos and diesel exhaust [57,58].

3.3.3. Bronchioloalveolar carcinoma of the lung

No relevant data identified.

3.3.4. Epithelial tumors of the thymus

No relevant data identified.

3.3.5. Mesothelioma*

Asbestos, erionite and painting are IARC group 1 carcinogens for mesothelioma with sufficient evidence [10]. Hundreds of studies have investigated the link between asbestos exposure and mesothelioma [3,59,60]. The first series of asbestos-associated pleural mesothelioma cases was reported in 1960 [61]. The risk for mesothelioma seems to be higher for some categories of fibers (amphiboles) [2].

3.4. Reproductive cancers

3.4.1. Mammary Paget's disease of the breast

No relevant data identified.

3.4.2. Epithelial tumors of the male breast**

IARC has concluded that shift work involving circadian disruption is associated with female breast cancer (limited evidence). Some occupations have been found to be at increased risk for male breast cancer, and exposure to electromagnetic fields [EMFs], polycyclic aromatic hydrocarbons, herbicides, pesticides, and organic solvents have been suggested to increase risk. Nevertheless, most studies focusing on specific exposures failed to find significant increases in associated risk [62]. However, an increase in risk was associated with gasoline motor exhaust [63]. More recently, male breast cancer was suggested to be associated with alkyl phenolic compounds that are endocrine disrupting chemicals [64].

3.4.3. Epithelial tumors of the cervix uteri**

Organic solvents (particularly trichloroethylene) are suggested to be the principal occupational exposure associated with cervical cancers [50,65]. Increased risk has also been

reported for exposure to metalworking fluids [66]. However, epidemiological studies that reported on this association did not adjust for well-known risk factors, including HPV. In addition, histological subtypes have not been well documented, and results have been inconsistent.

3.4.4. Adenocarcinoma of the ovary*

Ovarian cancer is one of the four cancers considered by the IARC to show sufficient evidence for association with asbestos exposure [67]. In addition, several other occupational exposures were shown to significantly increase the risk for ovarian cancer, including silica dust, diesel exhaust, and organic solvents; however, evidence is sparse [68–70]. Also, reports do not distinguish between histological subtypes of ovarian cancer.

3.4.5. Epithelial tumors of the vulva and vagina

No relevant data identified.

3.5. Urogenital cancers

3.5.1. Testicular cancer**

Several occupational exposures have been suggested to be associated with TGCT, such as EMF exposure, polychlorinated biphenyls, and pesticides. In addition, several occupations have been linked to TGCT, including agricultural workers, firemen, policemen, military personnel, and industrial workers (paper, plastic or metal). However, available evidence has not permitted the identification of strong and consistent occupational risk factors for TGCT [71]. Since testicular cancer occurs mainly in young adults, the potential impact of occupational exposure of mothers to endocrine disruptors during intra-uterine development has also been suggested [71,72]. However, data supporting this notion are sparse and inconsistent.

3.5.2. Extragonadal germ cell tumors

No relevant data identified.

3.5.3. Epithelial tumors of the penis

No relevant data identified.

3.5.4. Squamous cell carcinoma of the kidney

IARC has classified trichloroethylene as Group 1 carcinogen with sufficient evidence for kidney [10]. IARC concluded that there is a positive association (limited evidence) with arsenic and inorganic arsenic compounds, cadmium and cadmium compounds, and printing processes [10]. We did not identify any studies on this histology sub-type.

3.5.5. Non-transitional cell carcinoma of the urinary bladder

IARC has classified numerous occupational exposures as carcinogens (Group 1) for bladder (no distinction of histology subtype) with sufficient evidence (aluminum production, 4-aminobiphenyl, arsenic and inorganic arsenic

compounds, auramine production, benzidine, magenta production, 2-naphthylamine, painting, rubber production industry, ortho-toluidine, X-radiation, gamma-radiation) and limited evidence (4-chloro-ortho-toluidine, coal-tar pitch, diesel engine exhaust, dry cleaning, occupational exposure of hairdressers and barbers, printing processes, soot, textile manufacturing, tetrachloroethylene). Occupational risks for bladder cancer have been mainly evaluated in regard to transitional cell carcinoma; we did not identify any studies investigating occupational exposures in other histology subtypes (i.e., adenocarcinoma, squamous cell carcinoma).

3.5.6. Non-bladder urinary organs (renal pelvis, ureter, and urethra)*

IARC has classified aristochloric acids as carcinogenic for ureter and renal pelvis (sufficient evidence). Occupational risks for renal pelvis cancer (>90% transitional cell carcinoma) are those established for bladder cancer [73–75]. Associations have also been observed with exposure to coke, coal, asphalt, tar products, and certain refining industries (mineral oil, chemical, and petroleum) [75].

3.6. Neuroectodermic and mesodermic tumors

3.6.1. Malignant melanoma of the mucosa

No relevant data identified.

3.6.2. Epithelial tumors of the eye and adnexa*

IARC has classified welding with sufficient evidence and solar radiation with limited evidence for eye.

No occupational exposure study could be identified for this type of cancer, except for melanoma.

3.6.3. Malignant melanoma of the uvea*

IARC has classified welding with sufficient evidence and solar radiation with limited evidence for eye. Occupational exposure to ultraviolet radiation has been described to increase eye melanoma in workers exposed during outdoor occupational activities and welders [76–78].

3.6.4. Soft-tissue sarcoma (STS)*

IARC classified 2,3,7,8-tetrachlorodibenzopara-dioxin (Group 1) and polychlorophenols and their sodium salts (Group 2B) as carcinogenic for STS (limited evidence). We did not identify other occupational risk factors for this cancer site [79–81].

3.6.5. Bone sarcoma*

IARC has classified radium (Group 1) with sufficient evidence for association with bone sarcoma. An increased risk was shown mainly in radium-dial painters [9]. Also, epidemiological evidence supports an increased risk of bone cancer in plutonium workers [22]. Moreover, epidemiological studies indicated that bone sarcoma is associated with exposure to medical X- or gamma-radiation. However, large cohorts on nuclear workers failed to display increased risk for bone

sarcoma, mainly due to small doses of exposure [82]. Furthermore, an increased risk was reported for workers who had been exposed to pesticides at work [83].

3.6.6. *Glial tumors of the central nervous system***

IARC has classified radiofrequency electromagnetic field (including from wireless phones) as carcinogenic for the brain and central nervous system (Group 2B) [84], but our review did not identify data supporting association with occupational EMF exposure. Furthermore, low frequency EMF exposure has been suggested to increase the risk of glioma, but results have been inconsistent [85–88]. Glioma was suggested to be associated with farming activities and exposure to pesticides, but these findings have not been confirmed [89–93]. In addition, an increased risk of glioma was recently suggested in workers exposed to carbon tetrachloride [94].

3.6.7. *Malignant meningioma***

An increased risk of meningioma in workers exposed to lead has been described [95–97]. Also, an association between meningioma and EMF exposure was reported with inconsistent results [86–88], and evidence supporting meningioma risk and pesticides is conflicting [91,93].

3.7. *Neuroendocrine tumors*

No relevant data identified.

3.8. *Endocrine tumors*

3.8.1. *Carcinomas of the pituitary gland*

No relevant data identified.

3.8.2. *Carcinomas of the thyroid gland***

According to IARC, there is sufficient evidence that ionizing radiation causes thyroid cancer, but not for occupational exposures (except under conditions of exposure during nuclear accidents) [10]. However, some epidemiological studies have suggested an excess risk among subjects occupationally exposed to ionizing radiation [98–100]. An increased risk of thyroid cancer has also been reported in women exposed to organic solvents [101].

3.8.3. *Carcinomas of the parathyroid gland*

No relevant data identified.

3.8.4. *Carcinomas of the adrenal gland*

No relevant data identified.

3.9. *Lymphoid diseases*

IARC has concluded that there is a causal relationship between lymphoma and several carcinogens with sufficient evidence (rubber industry, 1,3-butadiene) or limited evidence (benzene, tetrachlorodibenzo-para-dioxin, polychlorinated biphenyls, ethylene oxide, trichloroethylene).

Below (Sections 3.9.2–3.9.6), we only report on subtype-specific associations.

3.9.1. *Hodgkin disease (HD)***

No strong association has been found with specific occupational exposures. Several studies and meta-analyses have suggested an association with pesticide exposure [102–104]. Also, studies have indicated an increased risk of HD associated with wood dust exposure or wood-related occupations [105,106]; however, data are inconsistent and evidence supporting a causal role of occupational wood dust exposure is lacking according to IARC. Meta-analyses showed no increased risk associated with occupational benzene or other solvent exposure [107]. Finally, elevated risk for HD, particularly nodular sclerosis, has been reported for subjects exposed to immunologically active agents [108].

3.9.2. *Acute lymphoblastic leukemia (ALL)**

According to IARC the relation of ALL and occupational benzene exposure is supported by limited evidence. The association is supported by meta-analyses evidence [107]. ALL is one of the main radiogenic leukemia subtypes, but epidemiological data on occupational radiation exposure is insufficient. Associations with occupational EMF exposure has been suggested [109], but evidence is also insufficient.

3.9.3. *Burkitt leukemia/lymphoma*

No relevant data identified.

3.9.4. *Cutaneous T cell lymphoma/mycosis fungoides***

Studies on occupational exposures that might be associated with this subtype are rare. However, associations have been suggested for occupational hydrocarbon and sun exposure [110–112].

3.9.5. *Other T cell lymphomas and NK cell neoplasms***

Studies regarding other T cell lymphomas and occupational exposures are sparse. Data from the European Epilymph study did not support association with solvent exposure [113].

3.9.6. *Diffuse large B-cell lymphoma (DLCLB)* and follicular B lymphoma (FL)**

Occupational benzene exposure was found to be positively associated with DLBCL and FL in several studies, although the relationship was not significant in all studies [114–118]. Overall, a positive association with solvents has been reported [113,115,117,119,120], although this appears to be more consistent for FL than for DLBCL. Also, an association of DLBCL with formaldehyde exposure was suggested [117]. For FL, a significant association with combined exposure to benzene, toluene, and xylene has been reported [113]. Furthermore, FL has been linked to occupational pesticide exposure [102,121].

3.9.7. Hairy cell leukemia (HCL)**

No strong association has been shown with occupational exposures. A positive association was suggested for farming [102,122,123]. So far, the evidence linking organic solvents and exhaust fumes to HCL has been insufficient.

3.9.8. Multiple myeloma (MM)*

According to IARC, a positive association of MM with benzene exposure exists (limited evidence), supported by epidemiology studies [124–127]. Furthermore, IARC concluded that there is a positive association with ethylene oxide exposure (limited evidence). A consistent, but modest, increased risk of multiple myeloma has been suggested for occupational pesticides exposure [73,102,128–130]. Residents and/or workers of sheep farms have shown an increased risk of MM, indicating that certain animal viruses may be involved. Moreover, a meta-analysis has suggested an association with engine exhaust [127]. An inconsistent association has been shown with chlorinated solvents [113,115,131] and for work in the rubber industry [126]. Finally, associations with occupational exposure to TCDD, formaldehyde, and radiation have been reported [126,132,133].

3.9.9. Other non-Hodgkin, mature B cell lymphoma

3.9.9.1. Chronic lymphocytic leukemia (CLL)*/small lymphocytic lymphoma (SLL).** IARC concluded that there is a positive association (limited evidence) with benzene and ethylene oxide exposure [126]. Three meta-analyses have reported on elevated CLL risk associated with occupational exposure to benzene, but the findings were not significant in two of them [107,134,135]. The association with ethylene oxide exposure is supported by some epidemiological findings [136]. Moreover, a positive association with other solvents has been reported for CLL and SLL [113,120,137], but overall the results are inconsistent [117,119,135]. Furthermore, an increase in CLL risk has been reported for occupational 1,3-butadiene exposure [138]. A positive association was identified with occupational exposure to several classes of pesticides, but evidence also remains insufficient for these findings [102,139,140]. Recent studies have suggested an association with low doses of external ionizing radiation, but again the evidence was inconsistent [133,141–143]. Finally, a meta-analysis reported a non-significant increase in risk associated with EMF exposure [109].

3.9.9.2. Marginal zone lymphoma/MALT lymphoma**.

Evidence for association of these types of lymphomas with occupational exposure is sparse; however, an association with chlorinated solvents has been suggested [115]. Occupational animal exposure has also been linked with ocular adnexal marginal zone B-cell lymphoma, but the evidence remains insufficient [144].

3.9.9.3. Mantle cell lymphoma/centrocytic lymphoma. No relevant data identified.

3.9.9.4. Lymphoplasmacytic lymphoma/macroglobulinaemia Waldenstrom. No relevant data identified.

3.10. Acute myeloid leukemia (AML)*

IARC concluded that there is sufficient evidence for a causal relationship between AML and benzene exposure [124,126,134]. Moreover, IARC concluded that there is sufficient evidence for a causal link between leukemia and formaldehyde exposure [126]. Evidence from meta-analyses support the associations of AML with both, benzene and formaldehyde [124,126,132,134]. Furthermore, a positive association was found with 1,3-butadiene exposure, with a significant dose–response relationship [126], results not confirmed by a recent study [138]. AML is a radiogenic subtype [22], and an increased risk has been shown in a cohort of US nuclear workers [145]. Meta-analyses have indicated an increased risk associated with occupational exposure to pesticides [146]. Furthermore, an increased risk among workers exposed to diesel exhaust has been suggested [147], but the findings are inconsistent. Additionally, some studies have suggested a positive association with EMF exposure, but evidence for this remains insufficient [109].

3.11. Myeloproliferative neoplasms

3.11.1. Chronic myeloid leukemia*

The IARC concluded that there was sufficient evidence to support a causal relationship between formaldehyde exposure and myeloproliferative neoplasms [126]. Evidence from meta-analyses supports this association [132]. Moreover, according to IARC, there is sufficient evidence that ionizing radiation causes leukemia. CML is a radiogenic subtype and positive associations have been observed [22]. Numerous epidemiologic studies and meta-analyses have investigated the association of CML with benzene exposure, reporting inconsistent results [124,134,135,148,149]. The most recent meta-analyses provides solid arguments for increasing relative risks with increasing exposure assessment quality [124]. Also, associations have been suggested for occupational exposure to pesticides [146]. Data regarding association with 1,3-butadiene are inconsistent [138,150].

3.11.2. Other myeloproliferative and myelodysplastic neoplasms**

Although data linking occupational factors to other myeloproliferative and myelodysplastic neoplasms is sparse, associations with benzene, pesticides, and radiation have been suggested [135,151,152].

3.12. Histiocytic and dendritic cell neoplasms

No relevant data identified.

3.13. Childhood cancer

3.13.1. Childhood leukemia (CL)*

IARC concluded that there is a positive association between maternal exposure to painting and childhood leukemia (limited evidence). In numerous case–control studies, a positive association was reported between maternal exposure to painting (including pre-conception and during pregnancy) and AML (myelocytic, myelogenous, or non-lymphoblastic leukemia) or ALL (lymphoblastic or lymphoid leukemia) in offspring [153–157]. In contrast, the association with paternal exposure to paints has been inconsistent for both ALL and AML [153–155,157–161]. Also, three meta-analyses [162–164] have reported an increased risk of CL associated with parental exposure to pesticides; however, the leukemia subtype, exposure, and periods considered differed among the studies. Moreover, an association between CL and parental exposure to benzene and solvents has been suggested [155,158,159,165–169]. However, evidence on solvent exposure before conception has been inconsistent. While prenatal exposure to ionizing radiation, mainly through maternal medical exams, has been shown to cause CL [126], studies regarding maternal or paternal occupational radiation exposure (pre-conception or during pregnancy) and CL risk have shown inconsistent results [168,170,171]. Furthermore, data related to parental occupational EMF exposure have been inconsistent, and overall suggested a lack of association, in coherence with IARC monographs [161,168,172–174]. Finally, other factors that are suggested to be linked to CL include exposure to motor exhaust fumes, plastic materials, or woodwork (father). Nevertheless, it is impossible to draw any firm conclusions from these data.

3.13.2. Lymphoma*

A meta-analysis has suggested increased risk associated with parental exposure to pesticides [164]. Also, an increased risk of non-Hodgkin's lymphoma was suggested with maternal exposure to oil products, unspecified chemicals [168], and ionizing radiation [170].

3.13.3. Childhood brain tumors (CBT)*

A meta-analysis and two large scale registry-based cohort studies found a significantly increased risk of CBT for paternal [160,164] or parental [175] occupational pesticide exposure. Moreover, differences according to histological subtype were found (i.e., a positive association was reported for astrocytoma, whereas no association was found with primitive neuroectodermal tumors [PNET]) [176,177]. Maternal pesticide exposure was inconsistently found. Evidence also suggested an association between CBT and parental occupational exposure to polycyclic aromatic hydrocarbons (PAH) [178,179], paint [160], and diesel exhaust [180]. Furthermore, some parental occupations were associated with an increased risk of CBT, including mechanics or

drivers [181], chemical industry employees [182,183], and electrical workers [182].

3.13.4. Neuroblastoma**

A meta-analysis suggested increased risk associated with parental occupational pesticide exposure [164], but the evidence in support of this is insufficient. Data related to other parental occupational exposures are sparse and inconsistent, so conclusions cannot be drawn [184,185].

3.13.5. Ewing sarcoma*

Meta-analyses reported a significant increase in risk of Ewing sarcoma associated with paternal occupational pesticide exposure or farm work [164,186]; however, the data regarding maternal exposure to these factors were divergent. Evidence related to Ewing sarcoma and other parental occupational exposures is sparse and inconsistent [187].

3.13.6. Wilms' tumor**

Current meta-analyses do not support an association of Wilms' tumor with parental occupational exposure to pesticides [164]. Evidence related to Wilms' tumor and other parental occupational exposures is sparse and inconsistent [188].

3.13.7. Other childhood cancer**

Parental occupational exposure in other childhood cancers has been poorly studied. According to IARC a causal relation (sufficient evidence) exists between solid childhood cancer and prenatal radiation exposure, in Japanese A-bomb survivors and through medical exams. However, data on parental occupational radiation exposure are insufficient.

4. Discussion

Improving prevention and clinical management of rare cancers are important goals in cancer control. To our knowledge, this is the first comprehensive review on established and suspected occupational exposures associated with rare cancers. The term “rare cancer” recovers a heterogeneous group of malignancies, i.e., cancers of rare occurrence, rare histology subtypes and rare localizations of common tumors. Although the RARECARE rarity threshold (<6/100,000) might be considered too high, it has the advantage to be the subject of an international consensus [1], and provided a practical basis for selecting cancers for our review. The common histologic subtypes of lung and bladder cancer, the malignancies most often linked to occupational etiologies, were beyond the scope of this review because of their frequencies.

For 40% of the rare cancers included in our review, a positive association with exposure to occupational carcinogens is supported by IARC monographs and/or consistent evidence from epidemiology studies. However, for many others, the evidence is lacking or remains sparse and inconsistent.

The low incidence of rare cancers often constitutes a barrier to conducting adequately powered epidemiological studies. This could partly explain the inconsistent results reported [111]. Also, in many studies, not designed to investigate histologic subtypes, subtype-specific risk estimates are associated with large 95% confidence intervals and should be interpreted with caution [7,41,78,111]. Furthermore, positive associations might be due to chance when multiple testing is performed [189]. Although for some occupations the job title can be used as surrogate for occupational exposure (e.g., welders and welding fumes), the reliability of the exposure assessment might be limited for others (e.g., farmers). Also, heterogeneity of exposure definitions and exposure data collected might further explain inconsistencies across studies [190,191]. Furthermore, evolution of industrial practices could explain why some previously identified associations were not confirmed in more recent studies. Well-conducted meta-analyses can provide more solid evidence, in particular when individual studies are inconsistent or insufficiently powered, such as for parental pesticide exposure and risk of childhood leukemia [162–164]. This is why our review considered in priority evidence from meta-analyses.

Lack of subtype-specific histopathology details led to the exclusion of many studies. Also, advances in genetic and molecular biology have led to improvements in tumor subtyping (e.g., hematopoietic malignancies and sarcomas) and the evolution of classifications over time [192–194]. For example, the definition of NHL has evolved over the last decades and now includes previously distinct disorders (e.g., CLL, MM), analyzed separately in past epidemiological studies [193,194]. Furthermore, certain genetic polymorphisms of enzymes involved in xenobiotic metabolism may lead to augmented risk for some individuals [95,195]. However, such contributing factors were rarely considered in the reviewed studies.

In addition to epidemiology studies, IARC classification of human carcinogens takes into account animal and in vitro studies [196]. Thus, animal studies have confirmed that inhalation of asbestos fibers induces lung cancer and malignant mesothelioma, and several direct and indirect mechanisms have been proposed [197]. Likewise, animal studies and mechanistic evidence have shown that the genotoxic effects of benzene at the level of the pluripotent hematopoietic stem cells result in chromosomal changes. These are consistent with alterations seen in hematopoietic malignancies and circulating lymphocytes of benzene-exposed workers [198,199].

Our study presents several limitations. Given the objectives of our review, after careful review of the evidence for the 48 cancer sites for which relevant data were identified, we recorded occupational exposures supported by IARC classifications, meta-analyses or consistent evidence from several epidemiology studies. For selected articles, we retrieved the most relevant data and provided adjusted risks when available. Also, we reported occupational exposures inconsistently associated with a given cancer site or supported

by insufficient evidence. However given the wide range of cancers included in our review, it would have been impossible to record all studies with limited or negative results. Furthermore, the majority of publications in our review were identified through PubMed. While we can be confident that our combined search strategy enabled us to identify the relevant studies for a given cancer site, we did not perform a cross search for occupational exposures identified. Therefore we cannot exclude that some studies focusing on multiple cancer sites with negative results for a given cancer site, may have been ignored.

In conclusion, the main rare cancer sites with strong and consistent evidence were nasal, larynx, liver and ovarian cancer, mesothelioma, bone sarcoma, transitional cell carcinoma of non-bladder urinary organs and hematopoietic malignancies. The main exposures for these cancers were asbestos, wood dust, metals/metalloids, formaldehyde, benzene, vinyl chloride, and radiation. This review provides useful information to clinicians to pay greater attention to work-related exposures in patients with rare cancers. Five percent of cancers are of occupational origin [200], but occupational cancers remain largely under-reported with important spatial disparities [201,202]. The risk of not seeking compensation is significantly higher for women and the elderly [203]. Furthermore, care for people with occupational cancers represents an unnecessary financial burden and productivity loss [204]. Due to the latency between exposure and cancer development, work-related cancers often appear after retirement, making it important for clinicians to investigate the former occupations and exposures of elderly patients. Moreover, patients of the socio-professional categories that are most at risk frequently display considerable horizontal occupational mobility, resulting in multiple job-related exposures that they might overlook. In many countries, patients with certain cancers matching medical and exposure conditions can ask for compensation. In the European Union, the recognition of work-related cancers is based on a list of registered occupational diseases [205]. Although several rare cancers (i.e., mesothelioma, sinonasal cancer) with well-established work-related origins are registered on various national lists as occupationally related diseases, these classifications remain heterogeneous among countries.

Future research should focus on cancer sites such as NHL or the upper aerodigestive tract. In this regard, national and international collaborative studies should allow for more adequately powered epidemiological studies. Moreover, the accurate assessment of exposure remains a challenge [191]; therefore, more sophisticated methods for assessing exposure as well as genetic and molecular biology techniques for evaluating gene–environment interactions will be important for future epidemiologic research. For instance, we are currently conducting a case–control study on TGCT to investigate the association between TGCT risk and life-time exposure using combined methodologies, including job exposure matrices, geographical information system technology, analysis of

suspected genetic polymorphisms, and socio-economic risk factors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Reviewers

Derek Raghavan, Carolinas Health Care System, Levine Cancer Institute, Carolina, United States.

Gemma Gatta, Evaluative Epidemiology Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, I-20133 Milan, Italy.

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Biographies

Barbara Charbotel, MD, PhD, is an occupational physician specialized in occupational diseases and epidemiology.

She previously published several papers on occupational cancers and participated to the IARC monograph 106 on chlorinated solvents.

Béatrice Fervers, MD, PhD, associate professor, is a medical oncologist and holds a PhD in public health. She is the head of the Cancer and Environment Unit of the Léon Bérard Cancer Centre (Lyon, France) and has previously coordinated a national program in evidence-based knowledge translation in oncology.

Jean-Pierre Droz, MD, PhD, emeritus Professor of Medical Oncology at the Lyon-Est Medical School, Lyon University and former Chairman of the Department of Medical Oncology of the Centre Léon Bérard. His clinical research focuses on germ-cell tumors and prostate cancer, new drug development and geriatric oncology. The three authors have contributed substantially to the conception and design of this review, acquisition and interpretation of data, drafting the article or revising it critically for important intellectual content, and to the final approval of the version submitted.