Sawmill Chemicals and Carcinogenesis

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Workers in wood industries are exposed to variable medleys of chemicals, both natural and synthetic. Additional exposures include fungi, bacteria, bark and wood dusts, solvents, paints, and various other wood coatings. These individual and conglomerate exposures have been associated with diverse occupational illnesses and hazards, including cancers. In this commentary, I summarize both experimental and epidemiologic carcinogenesis results for several chemicals used in the wood industry, as well as for wood dust. Working in the wood industries entails excess risks of cancers, among other diseases and workplace injuries. A key to preventing occupationally and environmentally associated cancers, as in the wood industries, is avoiding exposures to chemicals and wood dusts and, in particular, chemicals known to cause cancer in animals or/and humans.
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Not only are workers in the sawmill and other wood industries exposed to a variety of natural chemicals, fungi, and bacteria in raw barks and woods, they are also exposed routinely to myriad and combinations of synthetic chemicals used in these wood and wood-related enterprises. As an example, in a paper on sawmill workers occupationally exposed to chlorophenate fungicides (*1*), no particular mention was made of experimental carcinogenicity studies of several chemicals that have been found to be pervasive in sawmill wood-working environs and the wood preservatives industry. Among many chemicals, these typically include chlorophenols, likely containing dioxin contaminants; creosotes; certain flame retardants; formaldehyde; metal salts (arsenic, chromium, copper); phenol; and various pesticides and fungicides. Without a doubt, most workers in the wood industries are exposed routinely and repetitiously to both natural and synthetic chemicals, and to wood and other dusts as well.

In this commentary, I summarize carcinogenesis results for several chemicals used in the wood industry, as well as for wood dust. Findings from experimental carcinogenesis studies in animals are not only important for ascertaining or confirming carcinogenic risks to humans (*2*–*5*) but for planning and performing etiologic epidemiologic studies as well (*6*). After all, we know that experimental carcinogenicity data are the prime indicators of potential carcinogenic hazards to humans (*7*–*11*). We also recognize that for all human carcinogens that have been tested in animals, there is a perfect correlation (*2,8,12*–*14*), and, significantly, for nearly one-third of the known human carcinogens, positive carcinogenesis findings in animals were first identified in experimental animals and only subsequently observed in humans (*15,16*). This alone surely represents a failure of the public health system, and one hopes that this will happen not at all or less so in the future. Of course, for some chemicals such as drugs and pesticides, toxicology studies are done typically before widespread human exposure occurs. Yet, even for chemicals in those two categories, they are often marketed despite having positive animal carcinogenicity or other toxicology information.

Using animal and human chemical carcinogenesis data and evaluative results, certain chemicals used in the wood industry should be considered logical and potential causal sources of occupational cancers. For example, studying children whose parents work in the sawmill industry, Heacock et al. (*1*) found only a small, nonsignificant association of childhood cancers for offspring of male workers exposed to chlorophenol fungicides and their dioxin contaminants. Hence, their "analyses provide little evidence to support a relationship between the risk of childhood cancer and paternal occupational exposure to chlorophenate fungicides in British Columbian sawmills" (*1*). However, Mirabelli et al. (*17*) did find an association between occupational exposure to chlorophenol and the risk of nasal and nasopharyngeal cancers in U.S. men 30–60 years of age.

In 1987, the International Agency for Research on Cancer (IARC) indicated that information on the occurrence of cancer in lumber and sawmill workers was limited (*18*). Specifically, nasal tumors, lymphomas and leukemias, and soft-tissue sarcomas have been linked with work in the lumber and sawmill industries, but the findings were considered inconsistent (*18,19*). Subsequently, the data on sawmill workers and cancer have become more abundant. In contrast, most of the available cohort and case–control studies of cancer of the nasal cavities and paranasal sinuses have shown increased risks associated with exposure to wood dust (*20*), and occupational exposures to wood dust are considered carcinogenic to humans. Moreover, employment in the furniture- and cabinet-making industry has been causally associated with nasal adenocarcinoma, as well as with an increased risk of other nasal cancers (*18*).

Wood Dust

Wood dust, generated in the processing of wood for diverse uses, is a complex substance and varies considerably according to species of tree and even geography. Composed mainly of cellulose, polyoses, and lignin, wood dust may contain a variety of nonpolar organic extractives (fatty acids, resin acids, waxes, alcohols, terpenes, sterols, steryl esters, and glycerols), polar organic extractives (tannins, flavonoids, quinones, and lignans), and water-soluble extractives (carbohydrates, alkaloids, proteins, and inorganic material) (*20*). Various chemicals are added to wood to impart hardiness, longer life, and resistance to pests, humidity, and other means of deterioration. Some of these added agents are the subjects of this communication. As an example, within the furniture-manufacturing industry, exposure may occur not only to dusts but to solvents and formaldehyde in glues and surface coatings. Manufacture of plywood and particle board may entail exposure to formaldehyde, solvents, phenol, wood preservatives, and engine exhausts. Exposures to chemicals in industries where other wood products are manufactured vary but are considered similar to those in the furniture-manufacturing industry.

Whereas the experimental studies of wood dust are considered inadequate for evaluation of carcinogenic risk, wood dust is carcinogenic to humans, causing cancer of the nasal cavities and paranasal sinuses (*20*–*22*). According to IARC, "The excess [in cancer] appears to be attributable to wood dust per se, rather than to other exposures in the workplace, since the excess was observed in various countries during different periods and among different occupational groups, and because direct exposures to other chemicals do not produce relative risks of the magnitude associated with exposure to wood

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dust"(*20*). These earlier findings have been further substantiated and provide strong support for the association between exposure to wood dust in a variety of occupations and the risk of sino-nasal adenocarcinoma, although less so for the occurrence of squamous cell carcinomas (*23*). Further, there is suggestive but inconclusive evidence for a causal role of occupational exposure to wood dust in cancers of the nasopharynx. Workers exposed to wood dust may have an excess risk of nasopharyngeal cancer and multiple myeloma in addition to sino-nasal cancer. Possible limitations tend to obscure relationships, rather than create false positive findings (*21*). Excesses of other cancers, including lung and stomach, have been reported among persons employed in wood industries or occupationally exposed to wood dust, but not as consistently or unequivocally.

In this paper, briefly presented in alphabetical order, are experimental carcinogenesis findings, with some remarks on human evidence, on several chemicals used or found in the sawmill industry: arsenic, chromated-copper-arsenate (CCA), creosotes, formaldehyde, pentachlorophenol, phenol, polychlorophenols, and tetrachlorodibenzo-*p*-dioxin (TCDD). More details on animal studies regarding exposure levels, body weights and mortality, and incidence rates of tumors can be found in the cited references, as can the epidemiologic evidence.

Arsenic

Arsenic has been long known to cause cancer in humans (*24,25*) and has been correlated convincingly with cancers of the skin, lungs, liver, kidney, and urinary bladder (*7,26,27*). In laboratory animals the findings have been considered less than adequate in that few studies have been done on arsenic and arsenic compounds, specifically arsenic trioxide, a common form of human exposures (*28,29*).

However, the two major metabolites of arsenics, DMAA (dimethylarsinic acid) and MMAA (monomethylarsinic acid), have been evaluated, and both have been shown to cause or promote cancer in rodents (*28–32*). Bioassays have been reported that show DMAA (cacodylic acid), typical of organic arsenicals, induced cancer of the urinary bladder in rodents, a site concordant with that seen in humans (*28*), and DMAA also promoted tumors of the urinary bladder as well as of several other organs: kidney, lung, liver, skin (fibrosarcomas), and thyroid glands in rats (*30–33*). MMAA promoted tumors of the urinary bladder in rats (*30*). This clearly indicates that humans and rodents possess a similar tendency to develop shared-site tumors when exposed to arsenicals.

Chromated-Copper-Arsenate

CCA is used worldwide for wood preservation, and it contains varying percentages of mixtures of arsenic pentoxide, chromium trioxide, and cupric oxide. Hexavalent chromium and arsenic trioxide are carcinogenic to animals and to humans (*7,18,28*), with chromium typically causing lung tumors and arsenic-inducing cancer in several sites (see "Arsenic"). No carcinogenicity studies on CCA per se were found, and no adequate reports on the carcinogenicity of copper or copper salts were located. Copper 8-hydroxyquinoline has been studied in animals but is considered deficient for evaluation.

Creosotes

Creosotes have worldwide use as wood preservatives. Creosotes contain a collection of polycyclic aromatic hydrocarbons. Potential hazards come from inhalation exposures and considerable opportunity for exposures to the skin. Creosotes, creosote oils, and anthracene oils were tested for carcinogenicity in mice by skin application, producing skin tumors, including carcinomas. One of the creosotes also produced lung tumors in mice after skin application (*18,34*). In a number of case reports, the development of skin cancer in workers exposed to creosote is described. Cutaneous epithelioma occurred in workers handling creosotes or creosoted wood during timber treatment. A mortality analysis of workers in many occupations indicated an increased risk of scrotal cancer for creosote-exposed brickmakers (*18,34–38*). This, of course, was the first identified chemical-caused occupational cancer, as described in 1775 by the surgeon Sir Percival Pott that chimney sweeps developed scrotal cancer as a direct consequence of exposure to a defined "substance" (soots) in their occupation (*39*). Environmentally, fish exposed in a creosote-polluted harbor (*40*) and river (*41*) developed liver tumors.

Formaldehyde

World production of formaldehyde is about 15 million metric tons, and this gas is used mainly in the production of phenolic, urea, melamine, and acetal resins, which have wide use in the production of adhesives and binders in the wood, plastics, textiles, leather, and related industries (*20,42*). Formaldehyde is used also as an aqueous solution disinfectant (formalin), embalming fluid, and preservative in many applications, particularly by anatomists and pathologists for tissues and organs. Formaldehyde occurs naturally in most living systems and in the environment. Nonoccupational sources include vehicle emissions, building materials, food, tobacco smoke, and use as a disinfectant. Several million people are exposed occupationally to formaldehyde in industrialized countries alone. Continuous relatively high-level exposures frequently exceeding 1 mg/m^3 have been measured in particle-board mills, during the varnishing of furniture and wooden floors, in foundries, during the finishing of textiles, and in fur processing. Other exposures include formaldehyde-based glues and varnishes, solvents, wood dust, wood preservatives, and textile finishing agents (*20,42*).

In experimental animals, exposure to formaldehyde by inhalation causes squamous-cell carcinomas of the nasal cavities. In drinking water studies, tumors were induced in the forestomach and gastrointestinal tract, as were leukemias (*20,42–44*). In humans, formaldehyde has been associated with nasopharyngeal cancers, and with squamous-cell carcinoma of the nasal cavities and paranasal sinuses (*20,42,45–49*). Further long-term occupational studies are obvious, including substantiation of cancers of the brain in anatomists and embalmers.

Pentachlorophenol

Pentachlorophenol (PCP), a member of the polychlorophenols chemical family, is a biocide used primarily as a wood preservative and as a herbicide, algaecide, defoliant, germicide, fungicide, and molluscicide. Toxicology and carcinogenesis studies of PCP were conducted by feeding diets containing a technical-grade composite or Dowicide EC-7 (a commercial grade with lower levels of contaminants) to groups of mice (*50,51*). Both technical PCP- and EC-7-related neoplasms were observed in three organs/systems: liver, adrenal gland medulla, and vascular endothelium (hemangiosarcomas). Results suggest that the carcinogenic responses were due almost exclusively to PCP, with possibly a minimal potentiating influence by contaminants, in particular hexachlorodibenzo-*p*-dioxins (*52*). Two-year feed studies in rats exposed to 99% pure PCP showed increased incidences of mesothelioma of the tunica vaginalis and nasal squamous cell carcinoma in male but not female rats (*53,54*).

Pentachlorophenol induced skin papillomas in the Tg.AC transgenic mouse model and not in p53+/- mice (*55*). Using the mouse cancer data (*50*), Reigner et al. (*56*) reported that risks of cancer for lifetime exposure to PCP are from 20 to 140 times greater than the acceptable extra risk (10^{-6}). IARC considers that there is sufficient evidence in experimental animals for the carcinogenicity of PCP, whereas there is limited evidence in humans for the carcinogenicity of combined exposures to polychlorophenols or to their sodium salts (*57,58*). Epidemiologic studies have shown significant associations with several types of cancer, but the most

consistent findings have been for soft-tissue sarcoma and non-Hodgkin lymphoma.

Phenol

Phenol, ranked in the top 50 chemicals produced in the United States with roughly 4–5 billion pounds, is used in the production of bisphenol A, caprolactam, phenolic resins (phenol formaldehyde), wood preservatives (PCP), chlorophenols, and several alkylphenols and xylenols (*59,60*). Phenol is also used in disinfectants and antiseptics. Occupational exposure to phenol has been reported during its production and use, as well as in the use of phenolic resins in the wood products industry. There is suggestive (one study) but inconsistent evidence for lung cancer risk among woodworkers exposed to phenol (*60*).

In male rats treated with phenol in drinking water, increased incidences of leukemia, pheochromocytomas of the adrenal gland, and c-cell carcinomas of the thyroid gland were found; however; these occurred only in the lower-dose group and not in high-dose male rats or in female rats or mice (*61,62*). Other than the data showing a carcinogenic effect of phenol in male rats, an explanation for these findings has not been forthcoming. Phenol has been shown to be a promoter in mouse skin exposure studies (*59*). Using Syrian hamster embryo (SHE) cells, phenol induced morphologic transformations, gene mutations at two loci (both ouabain-resistant and 6-thioguanine-resistant mutant frequencies were increased), chromosomal aberrations, sister chromatid exchanges, and unscheduled DNA synthesis (*63*). Obviously phenol is genotoxic.

Polychlorophenols

Di-, tri-, tetra-, and pentachlorophenols (see PCP above) might all be used in the wood industry or are products of other chlorophenols. Exposures to chlorophenols and their salts have occurred in their production, in the making of certain phenoxy acid herbicides, and in the wood, textile, and tannery industries (*58*). 2,4,5-Tri- and tetracholorphenols have not been tested adequately for carcinogenicity in animals. 2,4-Dichlorophenol, at exposures up to 10,000 ppm in the diet for 2 years, did not cause any increases in tumors in rats or mice (*64*). Interestingly, mononuclear cell leukemias in rats and lymphomas in mice were decreased in these studies. Conversely, 2,4,6-trichlorophenol induced mononuclear cell leukemias in male rats and liver tumors in mice (*65*).

Several case–control and cohort studies have shown significant associations with several types of cancer, with the most consistent findings being for soft-tissue sarcoma and non-Hodgkin lymphoma (*58*). A possible confounding effect of polychlorinated dibenzo-*p*-dioxins (see below), which occur as contaminants in chlorophenols, cannot be fully excluded. In humans, controlling for estimated formaldehyde and wood dust exposure did not alter the correlation between cancer and exposure, as much of the estimated chlorophenol exposure was among machinists (*17*). These findings support the hypothesis that occupational exposure to chlorophenol is a risk factor for nasal and nasopharyngeal cancer, although the role of machining-related exposures warrants further assessment (*17*).

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)

Dioxins are everywhere. They have been long known as being carcinogenic to laboratory animals, causing a wide range of tumors (*66–69*), and are now confirmed as being carcinogenic to humans (*7,67–72*). TCDD causes cancer in multiple species, multiple strains, both sexes, and in multiple organs and tissues (*66–69*). TCDD causes cancer by multiple routes, various durations of exposure, and ranges of exposure concentrations (*66*). Tumor responses in both animals and humans are varied and include (in decreasing order of confidence) total tumors, lung cancer, soft-tissue sarcoma, non-Hodgkin lymphoma, breast cancer, digestive system cancers, multiple myeloma, skin, and thyroid gland in humans; and (alphabetically) adrenal glands, hematopoietic system (lymphomas), liver, lung, mouth (tongue and hard palate), nasal turbinates (nose), skin, and thyroid gland in animals. Clearly, several dioxin-induced tumor sites are common in both humans and in animals. TCDD is another instance where the carcinogenesis findings were first identified in animals and only later in humans (*15*).

Summary

Certain chemicals used in the wood industry are carcinogenic to experimental animals and to humans. All of the chemicals reviewed in this commentary have been shown or reported to cause cancer. Carcinogenic organ sites are varied and are frequently the same in animals and in humans. Working in the wood industries certainly entails excess risks of cancers, among other diseases and workplace injuries. Of course, a key to preventing occupationally and environmentally associated cancers, such as in the wood industries, is avoiding exposures to chemicals, and in particular chemicals known to cause cancer in animals or/and humans (*73*). In the wood industry, as I am convinced is the same in most industries and for many cancers, etiologic factors are rarely single discrete agents, but are most likely associated with combinational effects as being the causes of a majority of cancers (*74*). This includes not only chemical exposures but also environmental conditions, individual genetic susceptibilities, and lifestyles. Unfortunately, however, animal bioassays, epidemiology studies, risk assessments, and regulatory actions typically center on individual agents. Almost singularly, IARC evaluates occupations, workplaces, and manufacturing processes for potential cancer causation. More of these types of composite evaluations need to be done. Today more than ever, regarding chemicals and cancer, preventing or reducing cancer incidences and mortalities depends significantly and necessarily on limiting or avoiding exposure to all known occupational, environmental, and animal carcinogens (*75,76*). Why would we think otherwise?

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