Cancer risk associated with pulp and paper mills: a review of occupational and community epidemiology

Colin L. Soskolne and Lee E. Sieswerda

Pulp and paper mills use a variety of chemical substances potentially hazardous to human health. Compounds of both short- and long-term toxicological significance are found in workplaces, air emissions, and water effluent. In this paper we evaluate the body of published literature on cancer associated with working in pulp and paper mills as well as in surrounding communities.

Multiple comparisons, questionable statistical power, and the absence of individual exposure assessments have resulted in non-corroborative findings over the years. However, a new generation of study sophistication, international in scale and coordinated by the International Agency for Research on Cancer (IARC), has catalogued tens of thousands of exposure measurements made at a large number of work stations within the pulp and paper industry, allowing for greatly improved individual-level exposure assessments. This approach reduces non-differential misclassification of exposure, increasing the power of these studies to detect exposure disease relationships, especially for rarer cancers.

While the ability to associate specific chemical exposures with cancer outcomes in the large IARC multinational cohort may yet help to resolve the status of some of the many chemicals not currently classifiable as to their carcinogenicity by IARC, this effort has, to date, not added significantly to knowledge. Of the three studies they have published to date, one involved a well-established carcinogen (asbestos) and another involved a mixture containing probable carcinogens (volatile organochlorines). While the asbestos study is somewhat unremarkable for finding an association with pleural cancer in the expected direction, the volatile organochlorine study may be most notable for failing to find an association between volatile organochlorine exposure and liver cancer, non-Hodgkin's lymphoma, or esophageal cancer, as some previous studies had found.

Nonetheless, given the known hazards and the potential for both environmental and human exposure by any of a number of pathways, vigilance on the part of governments for regulation and for ongoing workplace and environmental monitoring remains a health imperative.

Introduction

The importance of the pulp and paper industry in modern life is a result of the major role of paper and paper products in every area of human activity. However, like many industrial processes it has impacted our environment and our health. Health concerns include both occupational hazards and impacts on air, soil, and water that affect the health of communities in the vicinity of pulp and paper mills as well as of those communities downwind or downstream from mills.

In this paper, we provide some background on the pulp and paper industry, then review both the English-language published literature and accessible unpublished reports of the epidemiological and toxicological evidence relating to the contribution of the pulp and paper industry to cancer risk. The focus is on studies of cancer risk associated with having worked in the pulp and paper industry. In addition, we have reviewed what information is available on the effects of these industries on cancer risk in local communities.

Health implications of work in the pulp and paper industry were reviewed at the global level in 1998 in the International Labour Organization's Encyclopaedia of Occupational Health and Safety, prior to the current crop of studies.[1-5] In sum, workers have been exposed to mechanical and chemical pulping processes, the latter mainly split between kraft (or sulphate) and sulphite processes. Local community exposures include chlorinated organic compounds, polychlorinated dibenzodioxins, and polychlorinated dibenzofurans. In addition, respirable particles of lime and sulphates have been found in the ambient air surrounding pulp mills.

The chemicals used and produced by pulp and paper mills vary according to a number of factors, including the wood species, pulping processes, and bleaching processes used.

It should be noted that some of the chemicals to which workers have been exposed have been reduced or eliminated in recent years. Asbestos is an example of a substance that workers were exposed to in the past, but which is now largely eliminated in the developed world. Mill effluent has also been cleaned up in recent years. In Canada, strict new regulations on mill effluent came into effect in 1992, with subsequent reductions in environmental discharges.[6] However, cancer has a long latent period, so all of the exposures in the past century of pulp and paper making are of interest.

The production context

The component of interest in the manufacture of pulp and paper is cellulose. Cellulose is a long-chain carbohydrate composed of polymerized glucose. It forms strong fibres that are ideal for paper-making. To obtain the cellulose fibres, short-chain carbohydrates called hemicelluloses (which are combinations of sugars including glucose, mannose, galactose, xylose, and arabinose) must be removed. Compared to cellulose, the hemicelluloses are easily degraded and dissolved.

Woody plant materials also contain an amorphous, highly polymerized substance called lignin that forms an outer layer around the fibres and cements them together. Lignin is also contained within the fibre. The chemistry of lignin is complex. It consists primarily of phenyl propane units linked together in a three-dimensional structure. The linkages between the propane side chains and the benzene rings are broken during chemical pulping to release cellulose fibres. A number of additional substances (e.g., resin acids, fatty acids, turpenoid compounds, and alcohols) are present in native fibres, their exact constituents and proportions depending upon their plant source. Most of these compounds are soluble in water or in neutral solvents, and are collectively called extractives.

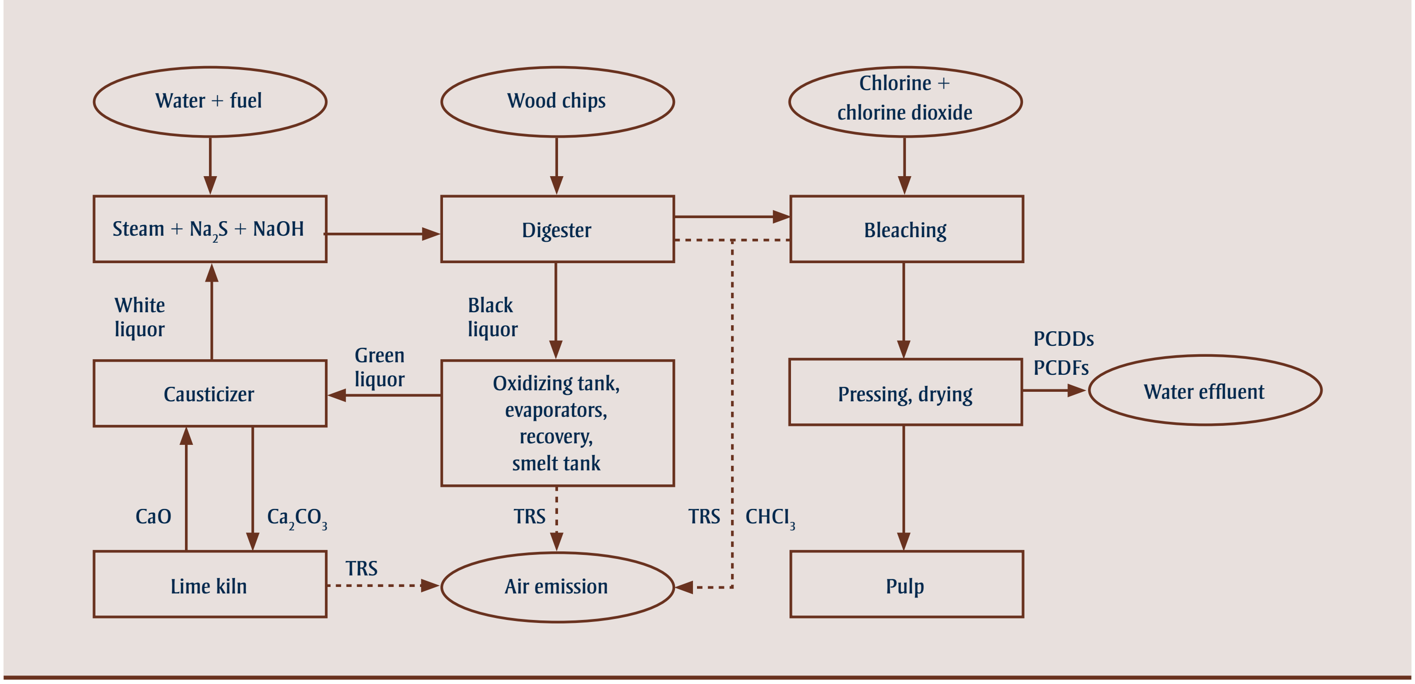
Pulp mills extract and process cellulose fibres from wood, simultaneously removing unwanted constituents, such as lignin. The two main types of pulping processes are mechanical and chemical. Mechanical pulping uses heat and mechanical forces to separate the wood fibres into a light-coloured pulp that requires little bleaching. Chemical pulping uses a mixture of chemicals to separate the cellulose fibres from the lignin. The two major chemical pulping processes are kraft (or sulphate) and sulphite.

Figure 1 is a simplified process diagram for a kraft mill. Kraft pulping is carried out in an alkaline medium and releases fibres from wood chips by dissolving the lignin in a caustic solution of sodium hydroxide and sodium sulphide. Spent digester fluid is concentrated in evaporators and fed into the recovery furnace, which recycles solid sodium sulphide and combusts the organic component as a source of energy. A lime kiln recovers calcium oxide for regeneration of the caustic component of the digester fluid.

In contrast, the sulphite process is carried out under acidic conditions and solubilizes lignin through sulfonation using a solution of sulphur dioxide and alkaline oxides such as sodium, magnesium, ammonium or calcium. The recovery of digester fluid components is accomplished by various means depending on the alkaline oxide used. Both chemical processes produce a relatively dark-coloured pulp that requires bleaching. The vast majority of the 47 bleached pulp mills operating in Canada through 1993 used the kraft method.[7] Five mills employed the sulphite process.

The resulting pulp is washed and bleached – in the past with elemental chlorine, today with chlorine dioxide and/or hydrogen peroxide. The washed pulp is rolled and dried, and the dried pulp is cut and baled for shipment. Several decades ago, wastewater from the bleaching process was typically discharged directly into a nearby body of water. Since about the 1960s, mills were required to perform primary treatment of effluent (i.e., settling out of large particulates before discharge). Today, however, Canadian mills are required by federal regulations to perform secondary treatment in addition. Most mills in Canada use aerated stabilization basins or activated sludge to remove oxygen-consuming materials and decrease the effluent toxicity, and this toxicity is monitored.[8]

FIGURE 1
Simplified diagram of the kraft pulping process



Variations in wood species

Moving across Canada geographically from west to east, there are four major forest land formations: the Pacific Coastal Complex, the Rocky Mountain Complex, the Boreal Forests, and the Eastern Deciduous Forests. Depending on the raw material (i.e., tree species) used in pulp and paper production, different environmental and occupational exposures will result.

Botanically, woods are classified into two main groups: the gymnosperms are the softwoods, conifers or evergreens; the angiosperms are the hardwoods – either deciduous or broad-leaved trees. The different wood species used in pulping require different types and quantities of chemicals, different in-plant processes and result in different by-products and product properties.

Generally, hardwoods contain a larger proportion of cellulose and hemicellulose and less lignin, as compared to softwoods, but a greater percentage of extractives. In addition, hardwood effluent contains chlorinated syringols. In general, softwood produces greater quantities of phenolic compounds than hardwood. Softwood effluent, chlorinated in the bleaching process, contains chlorophenols, chloroguaiacols and chlorovanillins.

Epidemiological studies of pulp and paper mill workers

Exposure of pulp and paper mill workers to potentially hazardous materials may arise at any stage in the process, from preparation of the raw wood through the production of the final pulp or paper product (Table 1). Wood preparation does not differ substantially for the several processes, but there can be significant differences in exposures in subsequent process steps, including cooking liquor production, pulp production, washing, bleaching, recovery, and paper making.

Most exposure studies in pulp and papermaking are of gaseous sulphur compounds, chlorine and chlorine dioxide. Though they have been shown to have significant respiratory and cardiovascular effects, these sulphur compounds have not been shown to be carcinogenic. In addition, vapours emanating from pulp may contain terpenes, sodium hydroxide mist, methanol, ethanol, sulphuric acid, furfural, hydroxymethylfurfural, acetic acid, formic acid, gluconic acid, hydrogen peroxide and many other potentially hazardous compounds. Dusts consisting of lime and sodium sulphate (among others) are also present and pose a potential exposure risk during the chemical recovery process.[9] Long-term exposure to fine particulate matter ($PM_{2.5}$) such as this is thought to cause lung cancer.[10] Pesticides used for control of slime and algae also constitute potentially harmful exposures. Exposure to complex chlorinated organic compounds, some of which are probable carcinogens, may occur through contact with slimicides (e.g., pentachlorophenol), pesticide-treated wood, or compounds formed during the bleaching process. Welders are exposed to hexavalent chromium in stainless steel welding. Perhaps most importantly from a cancer risk perspective, in the past workers (especially maintenance workers) were commonly exposed to asbestos.

Important challenges in occupational cancer studies

Workers represent a well-defined group of people for epidemiological assessment. The occupational health status of pulp and paper mill workers has been studied for a variety of endpoints, including cancer, pulmonary function, skin diseases, and

TABLE 1
Occupational exposures in the pulp and paper industry

Production area/job	Potential exposures
Raw wood preparation (i.e., debarking, chipping)	Wood volatiles, wood dust, spores, fungi, microbes
Production of cooking liquor	***Sulphate:*** ammonia, hydrogen sulphide, sulphur dioxide, mercaptan, chromate and other contaminants
	Sulphite: sulphur, sulphur dioxide, calcium carbonate, zinc, sulphuric acid, lead fumes, asbestos, sulphurous acid
Pulp production, cooking	***Sulphate:*** lime, magnesium, wood volatiles
	Sulphite: pigments, dyes, wood volatiles
	Ground wood: wood volatiles, aniline
Pulp bleaching, bleach plant	Chlorine compounds, ozone, hydrogen peroxide, boron compounds, caustic acids
Wet pulp, paper additives	Talc, clays, titanium dioxide, urea and melamine formaldehyde, pigments, dyes
Paper rolling, sizing, dying, drying, glazing, coating	Urea and melamine formaldehyde, paper dust, coating and pigment dusts
Maintenance	General plant exposures, asbestos, welding fumes
Unknown jobs, power, utility	General plant exposures, asbestos
Unexposed jobs	No significant exposures

hearing impairment. For some endpoints, such as cancer and respiratory effects, findings have varied considerably across studies.

Exposure assessment has been a significant issue in past studies. Lacking measurement of exposure to specific chemicals, most cohort studies have divided workers into at least three exposure categories: those who work in a paper mill, a sulphate (kraft) pulp mill, or a sulphite pulp mill. For simplicity, workers usually are categorized according to the last job they held, and exposure is defined as duration of employment. This surrogate exposure assessment is crude and may be problematic if the person has performed different jobs over his or her lifetime. Inadequate exposure assessment and other methodological problems in the generation of studies prior to about the mid-1990s, have resulted in controversy over their interpretation.

Efforts are being made to improve exposure assessment,[11-15] which would permit more valid classification of workers for study purposes. Of particular note is the more recent large international effort to take new, detailed measurements of specific chemicals across the spectrum of jobs in the pulp and paper industry, and to integrate them with all known previous measurements dating back to the 1950s.[13-15] Such detailed measurements have yielded more comprehensive job-exposure matrices and more accurate and specific exposure assessments.

In addition to the ongoing challenge of exposure assessment, there is another significant and related challenge that will become obvious in our review of the occupational cohort studies in the pulp and paper industry: choosing an appropriate comparison group. Most of the cohort studies that we have reviewed report the standardized mortality (or incidence) ratio (SMR or SIR) as their measure of effect. These measures compare mortality rates (or disease incidence) in the study cohort to the general population while simultaneously accounting for discrepancies in the age distribution of the two groups. The SMR and SIR have a number of advantages and disadvantages, but the chief disadvantage in the studies we review is its susceptibility to the healthy worker effect.

The healthy worker effect (HWE) is a form of bias caused by the fact that people who become sick or are especially sensitive to exposures in a particular workplace are not likely to start or continue employment at that workplace. Thus, occupational cohorts tend to be made up of quite healthy or resistant individuals compared to the general population. Especially when studying relatively subtle associations, the difference in the general robustness of the workforce compared to the general population can make it difficult to detect the effect of toxic exposures on health. Indeed, in a review of 270 occupational cohort studies, Meijers et al.[16] found that most exhibited a HWE (mean SMR: 84) which had a large influence on the study findings, tending to turn what might have been statistically significant positive findings into negative or equivocal findings. The effect was especially prominent among those studies involving chemical exposures. Unfortunately, the HWE is difficult to control and is not easily distinguished from other possible explanations (like genuine protective effects). Arrighi and Hertz-Picciotto[17] have reviewed methods for avoiding or correcting for the HWE, but these methods were not used in the older studies we review below. Some of the newer studies have avoided the problem by choosing a non-exposed group of workers (e.g., administrative office workers), rather than the general population, as the comparison group.

Another methodological challenge that arises frequently in occupational cancer studies is the problem of multiple comparisons. It is not uncommon for investigators to search for excess risks among up to 30 different cancer sites, frequently over three or more exposure categories and two or more latency periods. Thus, many papers essentially involve a search for statistical significance across 200 or more comparisons. Yet, although one would expect as many as ten statistically significant results to occur by chance alone (at the 95% level of significance), almost never is a statistical or interpretive adjustment made for this problem.

Case-control and proportional mortality studies

Thirty-two case-control and proportional mortality studies have presented some data on cancer risk among pulp and paper workers.[18-49] Occupation was usually abstracted from death certificates or from cancer registries. The occupational groups in most of these studies were broad.

The case-control and proportional mortality studies revealed few statistically significant associations between cancer and working in the pulp and paper industry. The case-control studies were generally much weaker than the cohort studies reviewed below, largely because most did not attempt detailed exposure assessment. Most of the studies referred only to the pulp and paper industry in general, or to production versus non-production workers, and did not separate the workers by process. This is problematic because the exposures are quite variable among the different processes.

Lung and pleural cancers have been of significant interest to researchers of pulp and paper workers. In a study designed to avoid the healthy-worker bias, Menck and Henderson found a significantly increased risk of lung cancer among paper workers (SMR = 171, where the denominator included only working people).[31] In a relatively weak study design, Harrington et al. found a statistically elevated risk of lung cancer (OR = 3.3) in non-urban counties where pulp and paper was the major industry.[28] In a death certificate analysis of counties in Louisiana, Gottlieb et al. found no increased risk of lung cancer among either pulp and paper workers or residents living near pulp and paper mills.[26] Toren et al. found no increased risk of lung cancer among pulp and paper production workers, but did find a statistically significant increased risk (OR = 2.1) among maintenance workers.[46] Wingren et al. found no statistically significant increased risk, except for the poorly defined group of secondary tumours.[49] In a study of sulphate mill workers that used the surrounding communities as referents, with exposure assessment, Andersson et al. found a significantly elevated risk for both pleural and lung cancers (OR = 9.5 and 1.6 respectively).[18] The authors attributed these increases mainly to past asbestos exposure. This study also found significantly elevated risks of brain, liver, and biliary tract cancers, as well as leukemia in the soda recovery plant, the bleaching plant, and the digester house. In a case-control study nested within their ongoing Polish pulp and paper cohort, Szadkowska-Stanczyk and Szymczak found a statistically significant, dose-response relationship between lung cancer and exposure to inorganic dusts, even after adjustment for smoking status.[44] They also found an elevated rate of lung cancer among those exposed to wood dust (a known carcinogen), but it failed to achieve statistical significance.

Other cancers of note in case-control studies have included lymphomas, bladder cancer, and cancers of the reproductive organs. In a very early study using death certificates, Milham and Hesser demonstrated a statistically increased mortality rate from Hodgkin's disease among woodworkers.[32] In a New Zealand cancer registry study, Pearce et al. could find no statistically significant association between testicular cancer and working in the pulp and paper industry.[38] However, two years later the same data showed a slightly increased risk of Hodgkin's disease.[50] Using British Columbia (BC) cancer registry data, Band et al. found a greatly increased risk in the pulp and paper industry of non-Hodgkin's lymphoma (OR = 10), but the risk estimate was based on only five cases.[19]

Also using BC cancer registry data, Teschke et al. found no significant increases in either nasal or bladder cancer among pulp and paper workers.[45] Ugnat et al., in a case-control study of bladder cancer among chemical workers in Western Canada that included some pulp and paper workers, found an elevated, but not statistically significant, risk of bladder cancer among pulp and paper workers (OR = 2.33, 95% CI:0.75,7.25, after controlling for province, age, pack-years of smoking, education, exposure-years, coffee and tea consumption).[47] In a recent study, Cocco et al. examined death certificates in 24 US states to assess occupational risk factors for gastric cardia carcinomas.[22] A statistically significant odds ratio of 2.0 was found for pulp and paper workers. In one of the few studies of women in the pulp and paper industry, Langseth and Kjaerheim used a case-control design to look for an increased risk of ovarian cancer among (mostly administrative) workers.[30] No significant relationships were found between ovarian cancer and asbestos, talc, or total dust exposure, which is probably reflective of the small number of women exposed.

Cohort studies

Cohort studies of pulp and paper workers have, in general, been more robust than case-control and proportional mortality studies. They have benefited from greater power and heterogeneity of exposure for comparison purposes. The earlier studies separated workers into (at least) paper mill, sulphate pulp, sulphite pulp exposure categories, while in more recent studies, chemical-specific exposure assessment by job classification across process types have been conducted. Like the case-control and proportional mortality studies, however, many of these cohort studies compare workers to the general population and therefore are susceptible to the HWE.

Twenty-four cohort studies of cancer among pulp and paper workers have appeared in the literature.[51-74] Tables 2 to 4 summarize the results of the fifteen cohort studies that provided specific risk estimates and that presented results according to the three exposure categories, paper mill, sulphate pulp, or sulphite pulp. Two of the published studies were not available in English and so are not reviewed here.[58,73] Overall, there were few statistically significant and many unrepeated results.

Among paper mill workers compared to the general population, (Table 2) a significant increase in cancer of the biliary tract was detected in one study[67] and an increase in lung cancer was found in another.[62] Smoking habits assessed by questionnaire did not explain the increase.[75] Two studies, one of incidence[56] and one of mortality,[57] found significantly fewer than the expected number of lung cancers. Coggon[57] also found a significantly more favourable overall cancer mortality experience among paper mill workers than the general population. These findings suggest a HWE. Langseth and Andersen found no significant cancer excess among paper mill workers, and was also notable for showing no evidence of a HWE.[65]

Cohort studies of sulphate (kraft) pulp mill workers found decreased risks of cancer more often than increased risks (Table 3). Both Robinson et al.[70] and Matanoski et al.[68] found significantly reduced overall cancer mortality among sulphate pulp workers relative to the general population. More specifically, Matanoski et al.[68] found significantly fewer deaths than expected from cancers of the pharynx, colon, rectum, pancreas, larynx and lung. However, a strong HWE appeared to be operating. Similarly, in 1997, Band et al. found a significantly decreased risk of mortality for stomach and pancreatic cancer.[53] A follow-up incidence study by Band et al. in 2001 found an excess risk of prostate cancer and melanoma among kraft mill workers.[54] A Polish cohort coordinated by Szadkowska-Stanczyk et al. also showed an elevated risk of prostate cancer mortality in a cohort with overall cancer mortality similar to the general population.[72,76]

Cohort studies in sulphite mills also have shown inconsistent results. Robinson and colleagues[70] found significantly lower cancer mortality among sulphite workers than in the general population (Table 4). In contrast, the much larger study by Band et al. in 1997 found an elevated overall risk of cancer.[53] Specifically, significantly increased risks of pancreatic, lung, and brain cancers were detected. The lung and pancreatic cancer findings were confirmed in a 2001 incidence study by Band et al., and an excess of liver cancer was added to the positive findings.[54]

Langseth and Andersen also found a statistically significant increase in lung cancer incidence among sulphite workers.[64] However, the authors suggest that most of the excess can, in fact, be attributed to smoking. This explanation cannot be excluded from Band's 2001 study either since he and his colleagues did not have data on their cohort's smoking status.[54] Band's 1997 study found fewer prostate cancers than expected among sulphite pulp workers, a finding not confirmed by his 2001 incidence study.[53] In another large study, Matanoski et al. found a significantly decreased risk of cancer.[68] She and her colleagues found fewer colon, lung, and brain cancer deaths than would be expected in the general population. This study seems to have suffered from the HWE. Henneberger and Lax constructed a Cox proportional hazards model to complement the more common SMR analysis.[61] In their study, an SMR of 95 was observed for lung cancer. However, after taking into account age at entry, smoking, and other factors, a hazard ratio of 2.5 (95% CI 1.3-4.9) was found, based on 35 observations. Henneberger and Lax stratified this model by length of work and found a hazard ratio of 1.9 (95% CI 0.8-4.4) for those with one to ten years of work experience, and 3.6 (95% CI 1.7-8.0) for those with more than ten years on the job.[61]

Several cohort studies have shown an increase in cancer among maintenance workers in pulp and paper mills. Jappinen et al. found nearly a doubling of risk for lung cancer among maintenance workers in paper mills.[62] McLean et al. showed a significantly increased lung cancer SIR of 1.44 (based on 36 cases) among non-production workers, but not other workers, in sulphate mills, suggesting that smoking was not the main causal factor.[69] The causal agent is thought to be asbestos, which has since been largely eliminated from pulp and paper mills in Canada. A recent study by Andersson et al. found that testicular cancer was significantly higher among maintenance workers than among process workers employed in both 1960 and 1970 in pulp and paper mills (SIR = 4.8, 95% CI: 1.3-12).[52] This is the only study to show such a finding and it was based on few cases, so it remains an hypothesis requiring confirmation.

By the early 1990s, it was becoming apparent that individual cohort studies were having difficulty providing clarity about the risks to pulp and paper workers. Many of the cancer excesses identified were found in only one or two studies and not confirmed by later studies. Indeed, it could be argued that with the large number of comparisons being made (owing to numerous cancer sites), and the small case numbers, chance could not really be excluded as an explanation for many of the excesses. Researchers in the field also came to realize that estimations of individual occupational exposure to specific chemicals should be carried out and used in future epidemiological studies in the industry.[77]

Because of these limitations, in 1991, the International Agency for Research on Cancer (IARC) initiated an international collaboration combining thirteen national cohorts of pulp and paper workers. The primary features of this collaboration are detailed exposure assessment for specific chemicals and large sample size. Chemical-specific exposure assessment allows specific exposure-outcome hypotheses to be tested, whereas older studies categorized exposure only by mill type and job classification. By establishing a large, standardized approach to the collection of data from as many participating centres around the world as possible, the potential to provide more definitive answers to the many questions about health risk would be increased. Three studies from this collaboration relating specific exposures to cancer outcomes have been published to date.[55,66,78] Because of the detailed exposure assessment in these studies, they are able to provide relative risks for the exposed versus the unexposed, as well as for any dose-response relationship within those exposed (Table 5).

As part of this IARC collaborative study, Carel et al. found that those with a high probability of ever having been exposed to asbestos were no more likely to die from lung cancer than those never exposed, but were more than twice as likely to die of pleural cancer (RR = 2.53, 95% CI: 1.03,6.23).[55] A positive dose-response relationship is suggested by the point estimates for both cancers, but statistical significance was not achieved. The relationship found between asbestos exposure and pleural cancer is not particularly surprising given that asbestos is a well-known human carcinogen.[79,80]

Another study from this IARC collaboration by Lee et al. examined the effect of exposure to sulphur dioxide and cancer mortality among workers in the pulp and paper industry.[66] Compared to unexposed workers, sulphur dioxide-exposed workers were significantly more likely to die from lung cancer (RR = 1.5, 95% CI:1.1,2.0). This study also found statistically significant dose-response relationships for all neoplasms, lung cancer, and non-Hodgkin's lymphoma. This study controlled for sex, age, employment status, calendar year, country, as well as occupational co-exposure to asbestos, combustion products and welding fumes. The authors did not, however, have information on smoking status or other lifestyle factors. This lack of smoking data plagued previous studies of sulphite mill workers exposed to sulphur dioxide and limited their interpretability. Finally, IARC does not currently consider sulphur dioxide to be a carcinogen,[81] so this finding will need to be confirmed by further research.

A third study from this IARC collaboration by McLean et al. examined the effect of exposure to organochlorine compounds.[78] Workers exposed to volatile organochlorine compounds were no more likely to die from any of the cancers studied compared to unexposed workers. However, within the exposed group, the authors noted a statistically significant dose-response relationship between volatile organochlorine compounds and all neoplasms.

To summarize the cohort studies to date, four major points can be made. First, many studies show a strong healthy worker bias, which may be masking potentially worrisome exposure-disease associations. Second, a weakness of many of these cohort studies is the reliance on mortality data rather than incidence data that could be obtained from a cancer registry. Cancer registries became more common only in the 1960s, and better incidence studies are beginning to appear. Third, until recently, exposure assessment has been weak. Finally, studies usually have included workers who have worked in pulp and paper for at least one year, and very few studies before 2000 considered length of employment in the analysis. Henneberger and Lax's Cox modelling shows the importance of taking length of exposure into account.[61] Many of the newer studies are including length of exposure, cumulative exposure and/or latency period in their analyses,[54,55,65,66,69,78] but many have

TABLE 2
Cohort studies of cancer risk among process workers in paper mills

	Malker et al. 1986[67]		Carstensen 1987[56]		Jappinen et al. 1987[62]		Henneberger et al. 1989[60]		Wong et al. 1996[74]		Sala-Serra et al. 1996[71]		Coggon et al. 1997[57]		Szadkowska-Stanczyk et al. 1997[72]		Szadkowska-Stanczyk et al. 1998[76]		Langseth & Anderson 2000[65]	
Years of follow-up	20		67		18		25		17		23		40		23		28[a]		40	
Type of risk estimate	SIR	(n)	SIR	(n)	SIR	(n)	SMR	(n)	SMR	(n)	SMR	(n)	SMR	(n)	SMR	(n)	SMR	(n)	SIR[b]	(n)
All cancers					121	-24	95	-32	85	-40	97	-37	77*	-220	58	-10	108	-31		
Biliary tract	180*	-25																		
Esophagus													104	-11	239	-1	278	-2		
Stomach					171	-5	198	-3	68	-1			68	-16			59	-2		
Colon							154	-5	125	-5	275	-4	60	-12			254	-2	110	-44
Rectum									242	-2			70	-8						
Pancreas							110	-2	44	-1			132	-15			84	-1		
Larynx													86	-2						
Lung			67*	(?)	197*	-12	81	-9	94	-17	57	-5	64*	-66	90	-5	166	-16	120	-81
Pleura																			160	-3
Skin melanoma									202	-2							310	-1	130	-21
Prostate									81	-2			103	-14						
Bladder									108	-1			84	-8	491	-2	270	-2		
Kidney							126	-1	80	-1			88	-5						
Brain													133	-8	131	-1	174	-2		
Non-Hodgkin's lymphoma													141	-8						
Hodgkin's disease													57	-1						
Multiple myeloma													133	-4						
Leukemia							241	-3	60	-1			119	-7			125	-1		
Breast											287	-3	64	-7						
Cervix													182	-4						
Ovary													30	-1						
Testis													226	-2						

SMR: Standardized mortality ratio

SIR: Standardized incidence ratio

* Significant at 95% level of confidence

[a] This information was obtained directly from the author in Oct. 2000 and is not explicitly presented in the 1998 paper.

[b] SIR refers only to "long-term" workers, i.e., those who worked in the pulp and paper industry ≥3 years.

TABLE 3
Cohort studies of cancer risk among process workers in sulphate (kraft) pulp mills

	Robinson et al. 1986[70]		Jappinen et al. 1987[62]		Sala-Serra et al. 1996[71]		Band et al. 1997[53]		Matanoski et al. 1998[68]	Szadkowska-Stanczyk et al. 1997[72]		Szadkowska-Stanczyk et al. 1998[76]		Langseth & Andersen 2000[65]		Band et al. 2001[54]	
Years of follow-up			18		23		42		22	23		28[b]		40		42	
Type of risk estimate	SMR	(n)	SIR	(n)	SMR	(n)	SMR	(n)	SMR[a]	SMR	(n)	SMR	(n)	SIR	(n)	SIR	(n)
All cancers	72*	-73	92	-54	102	-10	94	-439	82**	80	-20	110	-44			91*	-850
Oral cavity/ pharynx	29	-1					82	-11	52**	110	-1	68	-1			75	-25
Esophagus							112	-14	79							64	-8
Stomach	95	-6	87	-7			66*	-19	91	60	-2	82	-4			95	-34
Colon	22*	-2	192	-4	238	-1	110	-38	64**					120	-6	90	-68
Rectum							72	-12	81**			70	-1			61*	-30
Liver							57	-4	112	117	-1	63	-1			105	-8
Pancreas	36	-2					59*	-16	79**							64*	-16
Peritoneum												1716**	-2				
Larynx									40**	98	-1	59	-1			57*	-13
Lung	83	-25	87	-16	164	-4	100	-151	84**	85	-7	130	-18	140	-12	84*	-164
Pleura							251	-4						440	-1	178	-5
Bone							223	-4									
Skin melanoma							85	-7				458	-2	230	-4	155*	-45
Prostate	119	-8					131	-34	88	854**	-4	446**	-4			136*	-167
Bladder	125	-4	149	-3			119	-12	80			94	-1			73*	-41
Kidney							131	-17	95	151	-1	88	-1			84	-26
Brain							80	-17	101			199	-3			99	-23
Non-Hodgkin's lymphoma	207	-6					100	-16	118							107	-45
Hodgkin's disease									119							75	-10
Leukemia	24	-1					97	-19	93							92	-26
Testis									145			323	-1			92	-16

SMR: Standardized mortality ratio

SIR: Standardized incidence ratio

* Significant at 90% level of significance

** Signficant at 95% level of significance

[a] Cause-specific number of deaths not available; total deaths: 5,378

[b] This information was obtained directly from the author in Oct. 2000 and is not explicitly presented in the 1998 paper.

TABLE 4
Cohort studies of cancer risk among process workers in sulphite pulp mills

	Robinson et al. 1986[70]		Jappinen et al. 1987[62]		Henneberger et al. 1989[60]		Band et al. 1997[53]		Henneberger & Lax 1998[61]		Matanoski et al. 1998[68]	Langseth & Andersen 2000[65]		Band et al. 2001[54]	
Years of follow-up			18		25		42		25		22	40		42	
Type of risk estimate	SMR	(n)	SIR	(n)	SMR	(n)	SMR	(n)	SMR	(n)	SMR[a]	SIR	(n)	SIR	(n)
All cancers	79*	-88	105	-33	120	-36	114*	-351	108	-123	82**			117*	-464
Oral cavity/ pharynx							103	-7			105			91	-11
Esophagus							147	-11			86			126	-7
Stomach	149	-11	129	-6	72	-1	73	-19			78			94	-17
Colon	48	-5			102	-3	83	-21			71**	130	-23	98	-34
Rectum							121	-16			77			124	-27
Liver							199	-8			116			277*	-8
Pancreas	32	-2			305	-5	156*	-29	185	-11	74			177*	-21
Larynx									202	-3	55			133	-12
Lung	81	-26	90	-9	113	-11	132	-121	95	-35	79**	150**	-46	132*	-112
Pleura												240	-2		
Skin melanoma							172	-5				160	-10	139	-10
Prostate	111	-9			104	-3	67*	-19			108			111	-78
Bladder			270	-3			72	-7			110			87	-23
Kidney	148	-4			289	-2	143	-11			143			106	-12
Brain							172*	-16			34**			153	-10
Non-Hodgkin's lymphoma	133	-4					69	-6			89			91	-12
Hodgkin's disease							159	-4			40				
Multiple myeloma							171	-8						103	-5
Leukemia	67	-3			90	-1	51	-6			60			124	-14
Testis											86				

SMR: Standardized mortality ratio

SIR: Standardized incidence ratio

* Significant at 90% level of significance

** Signficant at 95% level of significance

a Cause-specific number of deaths not available; total deaths: 1,539 only enough data to dichotomize length of exposure, and the time periods reported are inconsistent making comparison difficult. Of these, only the latest studies by Lee et al.[66] and McLean et al.[78] had enough power to show statistically significant increased risks with increasing cumulative exposure.

The latest generation of cohort studies from the IARC collaboration are establishing more specific chemical-disease relationships. They have moved the focus away from trying to determine if working in the pulp and paper industry generally (or in particular mill types or job classes within mills) causes cancer. This older approach left the specific chemical exposure – disease relationship unspecified. Rather, the approach of the IARC collaboration involves measuring the specific chemicals that workers are exposed to and then associating the specific chemical exposures with cancer outcomes. These new exposure measurements are allowing for larger studies that combine workers having similar exposures, both within and across industries, in order to increase sample size.

This chemical exposure-specific approach has several advantages. First, knowing the specific exposure reduces nondifferential misclassification of exposure, thereby increasing the power of these studies to detect exposure-disease relationships. Second, it is not particularly helpful to workers or to industry to discover that simply working in the pulp and paper industry causes cancer. Rather, specific exposures need to be identified so that they can be remediated. Third, the ability to associate specific chemical exposures with cancer outcomes in a very large multinational cohort should help to resolve the status of some of the large number of chemicals not currently classifiable as to their carcinogenicity by IARC. Fourth, and finally, by being able to make comparisons both within and across industries (using relative risks as the measure of association as opposed to community-based standardized mortality or incidence ratios), the influence of any HWE is, for practical purposes, eliminated.

Epidemiological studies of communities near pulp and paper mills

Communities near pulp and paper mills are exposed to a different set of hazardous chemicals than pulp and paper workers. Their degree of exposure is, however, much more difficult to quantify.

Some data exist that quantify particulate matter in the ambient air surrounding pulp mills in British Columbia, with documented respiratory effects in children.[82]

Over 250 chlorinated compounds have been identified in pulp mill effluent.[83] In comparison with their non-chlorinated analogues, chlorinated organic compounds may become more toxic, more lipophilic and therefore bioaccumulative, less biodegradable, mutagenic and carcinogenic.[84,85]

Polychlorinated dibenzodioxins (dioxins, PCDDs) and polychlorinated dibenzofurans (furans, PCDFs) have received a lot of attention for their persistency and potential for accumulating in biological tissues.[86,87] One of the PCDDs, 2,3,7,8-tetrachlorobenzo-*para*-dioxin (TCDD) has been designated as a definite human carcinogen by the IARC.[88,p.33] PCDFs are not currently classifiable as to their carcinogenicity in humans, but an IARC review noted incidents in Taiwan and Japan of very high levels of exposure that may have resulted in liver cancer.[88,p.345] Both the respiratory tract and the skin can be routes of exposure for dioxins and furans.[89]

The major chlorinated hydrocarbon emitted into ambient air from bleached kraft pulp mills is chloroform, a possible carcinogen.[90] Other halogenated volatile organics that may become airborne as a result of evaporation from wastewater include trichloroethylene, tetrachloroethylene, carbon tetrachloride, dichloromethane, bromodichloromethane, and chlorodibromomethane. All of these compounds are mutagenic; the first five have tested positive in animal carcinogenicity bioassays, and some epidemiological evidence indicates that the first two are probably human carcinogens.

A number of studies in Canada, the USA, Scandinavia and other parts of the world have examined the health status of populations near pulp and paper mills.[20,21,35,40,91-97] Health endpoints examined have included acute and chronic respiratory diseases, cancer, mortality, hospital admissions, and a variety of annoyance symptoms (headaches, nausea, and eye and throat irritation). These studies implicate odorous pulp mill air emissions in the genesis of community annoyance reactions. Without personal exposure data, objectively determining exposures to various respiratory irritants is not possible.

Two ecologic studies[20,21] investigated lung and oral cancer mortality in US counties according to the proportion of the population employed in the pulp and paper industry. In a similar Canadian study,[40] excess all-cause male mortality was observed in six of 21 municipalities studied. Specifically, lung cancer elevations were noted in four of the 21 municipalities.

In the 1980s and early 1990s, community concerns in Canada about ambient levels of pollutants from pulp and paper mills resulted in two reports. One of these, a bibliography of related literature, assists further research in this area;[98] the other called for environmental regulatory reform.[99] These reports and others were heeded, and the Canadian government implemented new guidelines in 1992 to reduce pollution from pulp and paper mills.

Human health risk assessment and conclusions

Pulp and paper mills employing chlorine bleaching use a variety of substances potentially hazardous to human health. Compounds of both short- and long-term toxicological significance are found in the workplace environment. Air emissions and water effluent have been largely cleaned up in Canada since 1992, though surveillance continues and potential endocrine disrupting chemicals in the effluent need to be researched further. The presence of hazardous materials raises inevitable questions regarding worker health and safety, as well as the health of the general population.

TABLE 5
Selected relative risks from the latest generation of studies combining cohorts from 13 countries assembled under the auspices of IARC [rate ratio (95%CI)]

			Cancer site							
Study	Exposures studied	Exposure Categories	All Neoplasms	Lung	Pleura	Stomach	Non-Hodgkin Lymphoma	Esophagus	Liver	Lymphatic and Hematopoietic
Carel et al. 2002[55]	Asbestos	Ever vs. Never Exposed[a]	1.0 (1.0,1.1)	1.0 (0.8,1.1)	2.5 (1.0,6.2)					
		WCE in Ever Exposed								
		≤ 0.01 f/cc-year		Ref	Ref					
		0.02 - 0.09 f/cc-year		1.2	1.2					
		0.10 - 0.77 f/cc-year		1.4	1.7					
		≥ 0.78 f/cc-year		1.4	2.4					
		Test for trend:		$p = 0.07$	$p = 0.29$					
Lee et al. 2002[66]	Sulphur dioxide	Ever vs. Never Exposed[b]	1.0 (0.9,1.2)	1.5 (1.1,2.0)		0.7 (0.5,1.1)	2.6 (1.1,6.1)			2.5[c] (1.1,5.5)
		WCE in Ever Exposed								
		< 2.0 ppm-years	Ref	Ref		Ref	Ref			
		2.0 - 5.9 ppm-years	1.0	0.9		1.0	2.6			
		6.0 - 20.9 ppm-years	1.3	1.6		1.6	5.3			
		≥ 21.0 ppm-years	1.3	1.5		1.3	4.4			
		Test for trend:	$p = 0.001$	$p = 0.009$		$p = 0.3$	$p = 0.03$			
McLean et al. 2006[78]	Volatile organochlorines	Ever vs. Never Exposed[d]	0.99 (0.90,1.1)	1.1 (0.94,1.4)	1.1 (0.39,3.3)	0.76 (0.57,1.0)	0.79 (0.44,1.4)	0.68 (0.38,1.2)	0.75 (0.37,1.5)	0.95 (0.69,1.3)
		WCE in Ever Exposed								
		< 1 ppm-years	Ref	Ref	Ref		Ref	Ref	Ref	Ref
		1 - 17 ppm-years	1.1	1.2	1.2		1.2	0.94	1.1	1.1
		≥ 18 ppm-years	1.2	1.1	2.5		0.97	0.54	1.5	0.93
		Test for trend:	$p = 0.002$	$p = 0.39$	$p = 0.11$		$p = 0.96$	$p = 0.29$	$p = 0.53$	$p = 0.86$

WCE: Weighted cumulative exposure

Ref: Reference group

f/cc-year: Fibres per cubic centimeter-years

ppm-years: Parts per million-years

[a] Adjusted for country, age, calendar period, employment status

[b] Adjusted for sex, age, employment status, calendar year, country, exposure to asbestos, combustion products, and welding fumes

[c] Rate ratio for leukemia only

[d] Unadjusted model; we calculated the rate ratios using person-years from Table 1 and observed case counts from Table 2 in McLean et al. 2006.

Though recent monitoring reports[8] on pulp and paper mill effluent in Canada have been positive in that they show effective reductions in pollution, surveillance must continue. Many of the compounds produced by pulp and paper mills, especially chlorinated phenolics, dioxins and furans, are persistent in the environment, bioaccumulate readily in the food chain, and can contaminate drinking water.

Studies of pulp and paper mill workers and nearby communities have produced few conclusive results to date. Perhaps the most consistently found increased risk relates to lung and pleural cancers and asbestos exposure. Since the pulp and paper industry no longer uses asbestos, we expect the risk of lung and pleural cancers, as well as other respiratory morbidity related to asbestos exposure, to be eliminated; any remaining increases in lung cancer *per se* would be difficult to disentangle from smoking histories.

Various methodological limitations exist in the occupational studies, including potential ascertainment bias, the 'healthy-worker effect', and spurious correlations arising from multiple statistical comparisons. Although a number of occupational studies have suggested increased risk of cancer among workers, most have used the popular, but imprecise, standardized morbidity/mortality ratio (SMR) as the measure of effect. In the computation of SMRs, the standard set of weights is derived from the exposed population. Because indirect age-adjusted rates for different studies do not all use the same weighting factors (as would be true for directly adjusted rates), it is technically incorrect to compare SMRs from two or more studies. Thus, each indirectly adjusted rate is comparable only to the standard.

Large cohort and nested case-control studies with very good exposure assessment to distinguish exposed from non-exposed workers should serve to eliminate the need to use community-based SMRs as the measure of effect and to reduce the HWE. And finally, the philosophical and statistical problem of multiple comparisons is an issue that needs to be resolved. Because of the large number of comparisons made in most of the studies, and the lack of appropriate statistical adjustment, it is impossible to distinguish between any possible real associations and spurious relationships attributable to chance. This is unfortunate because methods could be applied to correct for this problem.

As for epidemiological studies of communities around pulp and paper mills, the studies are few and the ecological fallacy limits the interpretation of results. This bias may occur because an association observed between variables on an aggregate level may not represent the association that exists at an individual level.

The latest generation of IARC collaboration studies hold much promise. However, of the three studies they have published to date, one involved a well-established carcinogen (asbestos), another involved a mixture containing probable carcinogens (volatile organochlorines), and the third studied exposure to a substance not classifiable as a carcinogen (sulphur dioxide). While the asbestos study is somewhat unremarkable for finding an association with pleural cancer in the expected direction, the volatile organochlorine study may be most notable for failing to find an association between volatile organochlorine exposure and liver cancer, non-Hodgkin's lymphoma, or esophageal cancer, as some previous studies had found. The sulphur dioxide study may be more significant in that it may influence IARC's assessment of sulphur dioxide's carcinogenicity. However, perhaps the greatest impact from the IARC collaborative studies is that they have now made the proposition that "cancer is associated with working in the pulp and paper industry" almost obsolete. By studying specific exposures and relating them to the incidence of specific cancers, the focus has shifted to the concept of "cancer associated with a specific exposure." The fact that the exposure happens to be in the pulp and paper industry may be considered peripheral when one considers new discoveries about carcinogens. Of course, if such exposures happen to be an essential part of pulping and paper-making, then the discovery of ill-effects would continue to have profound implications for the industry.

As a final note, even with the large IARC cohort study, some cancers are so rare as to ensure that any definitive associations with specific exposures will remain speculative from an epidemiological perspective. Given these limitations, it may not be possible for epidemiological studies to demonstrate either association or causation. However, given the known hazards and the potential for both environmental and human exposure by any number of pathways, vigilance on the part of governments for regulation and ongoing workplace and environmental monitoring remains a health imperative.

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