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Strategic Information Memorandum (SIM 05-01)

TO: Canadian Corporate Correspondents

FROM: Kirsten Vice

SUBJECT: Cellulose Health Effects: Research and Regulatory Review

Cellulose is listed on Environment Canada's Domestic Substances List and is one of 23,000 DSL substances being "categorized" by Environment Canada and Health Canada to determine whether it could be assessed as "toxic" under the Canadian Environmental Protection Act. To date, it would appear unlikely that pulp cellulose will become listed as a CEPA toxic; however, an impending evaluation of cellulose by the International Agency for Cancer Research could result in stricter workplace exposure limits and more demanding product stewardship requirements.

<u>This material will interest pulp, paper, and paperboard facilities.</u>

The current area of interest with respect to the potential health effects of cellulose is related to the inhalation of cellulose fibres and in particular, the potential carcinogenicity of inhaled cellulose fibres. The health effects of cellulose related to exposure through injection are not covered in the attached report, as they are not particularly relevant to pulp and paper industry workplace environments or typical end-uses of paper products. The ingestion of cellulose products in various foods and pharmaceuticals is widespread and has been studied in depth, and many national health agencies, including Health Canada, have listed cellulose and a number of modified cellulose products as safe for consumption.

The current area of interest with respect to the potential health effects of cellulose is related to the inhalation of cellulose fibres and in particular, the potential carcinogenicity of inhaled cellulose fibres. There have been a number of published studies that have looked at the potential health effects of paper dust. When reviewing these studies, it is important to realize that, while cellulose is the principle component of paper, "paper dust" should not necessarily be considered to be the equivalent of "cellulose dust." For example, in work that NCASI has carried out on air samples from 10 different types of paper production facilities, it is estimated that between 25% and 95% of airborne dust must have been something other than cellulose.

Available evidence suggests that cellulose is a reasonably inert substance with low toxicity. Cellulose does not, however, appear to degrade once deposited inside the respiratory tract, and therefore, it is critical to keep worker exposures below the levels at which lung particle overload is likely to occur.

There is no evidence that inhalation exposures to cellulose dust result in the development of lung cancer of any type, but this area of research is by no means well developed. There have been no long-term inhalation studies at all and most of the short-term inhalation studies that have been conducted have used unrealistically high doses. Further, most of the studies that have been conducted using cellulose fibres have used routes of exposure that bear little resemblance to reality, leaving their relevance open to discussion.

There is an impending evaluation of cellulose by the International Agency for Cancer Research (IARC), which likely has the greatest potential to impact manufacturers of paper products. If IARC determines that cellulose fibres should be considered carcinogenic or likely to be carcinogenic in humans, this decision could set into motion reviews by various governmental health and safety agencies, possibly resulting in stricter workplace exposure limits and more demanding product stewardship requirements.

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Cellulose Health Effects:

Research and Regulatory Review

January 17, 2005

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Introduction

Cellulose is a polysaccharide, meaning that it is a polymer of repeating sugar units. Depending on the length of the polymer and the manner in which the strands of polymer aggregate, cellulose may be classified as a fibre or as a particle. Wood, in its native state, is 40 – 50% long-chain cellulose fibres (Smook, 2002). However, wood, wood chips, and wood dust are generally considered to be outside the scope of discussions about the health effects of cellulose and regulatory actions based upon those effects. In its native, unprocessed state, cellulose is embedded in a matrix of non-fibrous materials such as lignin, hemicelluloses, resins, and gums. Because "wood dust" is chemically and physically distinct from "cellulose," the health effects of wood dust are considered to be a separate issue from the health effects of cellulose.

Recent Cellulose Health Effects Research

Introduction

Research into the health effects of cellulose recognizes three potential routes of exposure: injection, ingestion, and inhalation. The health effects of cellulose related to exposure through injection are not covered in this report, since they are not particularly relevant to pulp and paper industry workplace environments or typical end-uses of paper products.

The ingestion of cellulose products in various foods and pharmaceuticals is widespread and has been studied in depth. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has evaluated a wide variety of cellulose and modified cellulose products that are used as food additives and has found them to be safe (e.g. JECFA 1975, 1997). Health Canada has listed cellulose and a number of modified cellulose products as safe for consumption, e.g. the "List of Acceptable Non-medicinal Ingredients." Similarly, the US Food and Drug Administration (FDA) lists a number of modified cellulose products as "Generally Recognized as Safe" food additives (US FDA, 2004).

The current area of interest with respect to the potential health effects of cellulose is related to the inhalation of cellulose fibres and in particular, the potential carcinogenicity of inhaled cellulose fibres. Therefore, the focus of the remainder of this review will be on inhalation exposures and related research. Within the pulp and paper industry, inhalation exposures to workers involved in papermaking are of greatest interest. Users of paper products are not likely to experience significant inhalation exposures, with the possible exception of individuals engaged in the installation of cellulose insulation.

There have been a number of studies published over the years that looked at the potential health effects of paper dust. When reviewing these studies, it is important to realize that, while cellulose is the principle component of paper, "paper dust" should not necessarily be considered to be the equivalent of "cellulose dust." For example, in air samples collected at 10 different types of paper production facilities, 5% to 75% of the airborne particulate matter collected in paper mills was organic, meaning that from 25% to 95% of the airborne dust must have been something other than cellulose (NCASI, 2004).

Health scientists generally classify cellulose as inert, insoluble particulate matter. For substances of this nature, toxicity is primarily associated with the physical properties of the particulate matter rather than the chemical nature of the substance. For nonfibrous inert, insoluble particles, toxicity is most often associated with the phenomenon of lung particle overload. When insoluble particulate matter is deposited in the lung, the particles are cleared from the respiratory tract

through the actions of alveolar macrophages and the mucociliary escalator. During chronic exposures to high concentrations of insoluble particles, the normal clearance mechanisms are overwhelmed, leading to a build-up of high lung burdens of particulate matter and the development of alveolar inflammation and fibrosis. Lung particle overload is most typically observed in experimental studies with rats and is considered to be a function of faulty experimental design, where exposure levels exceed lung clearance capacity. However, the effects of lung particle overload were not widely appreciated or researched until fairly recently. Many older studies used exposure levels at which lung overload occurred and thus led to biased conclusions about the potential health effects of the particulate matter being studied. The University of Rochester, Rochester, NY, has been the centre of research into the phenomenon of lung particle overload and scientists there have published several good reviews on the subject (e.g. Oberdorster, 1995 & 2002). In addition, in 1995, the Society of Toxicology held a workshop titled "The Maximum Tolerated Dose for Inhalation Bioassays: Toxicity vs Overload," in which the effect of inadvertent lung particle overload on the outcome of toxicity testing was discussed (Morrow, et al., 1996).

Typically, health-related research using cellulose focuses on the fibrous component of cellulose because experiences with asbestos have demonstrated that some insoluble fibres can be associated with unique carcinogenic effects. When asbestos fibres are inhaled and deposited in the lungs, shorter fibres are completely engulfed by alveolar macrophages and removed via the mucociliary escalator. Longer fibres, however, cannot be completely ingested by macrophages and thus become trapped, along with the macrophages that have attempted to engulf them, in the alveoli of the lungs. This triggers a chain of events that may ultimately result in asbestosis, lung cancer, or malignant mesothelioma. Fibre length and lack of solubility are not the only factors influencing the outcome of exposure to asbestos, though. The type of asbestos, the length of time the fibres remain in the lung, and the surface properties of the asbestos fibres all appear to be important elements in shaping the ultimate outcome. Whether or not cellulose fibres are likely to have any effects similar to those of asbestos has been the focus of much of the recent health effects research using cellulose fibres.

Studies of Soft Paper Mill Workers

During the 1970's and 1980's, researchers in Sweden conducted several studies of lung function and respiratory disease among workers exposed to paper dust in paper mills producing "soft" paper, which includes tissue, napkins, paper towels, and toilet paper. These mills used a significant proportion of recycled paper in their furnish. Ericcson et al. (1988) reported that workers with high exposures (> 5 mg/m^3) to paper dust reported more symptoms of upper respiratory tract irritation, including nasal congestion and dryness and irritation of the throat, than did workers with low exposures. There did not appear to be much difference in lower respiratory tract symptoms among workers with different exposure levels. The authors did report that workers with greater than 10 years of exposure to high levels of paper dust seemed to have reductions in lung function compared to workers with only short-term or low-level exposures. But, they noted that they were not able to adjust for the effects of smoking due to low sample size, and thus, the effects on lung function could have been related to smoking rather than paper dust exposure.

Jarvholm et al. (1988) compared the lung function of mill workers with high exposure (average $3.4 – 20$ mg/m^3) to paper dust to office workers at the same mill. All study participants were life-long nonsmokers. The researchers measured (or calculated) 11 different parameters related to lung function. Two of those parameters, elastic recoil pressure and residual lung volume, were significantly different in paper dust-exposed workers than in office workers, indicating a

reduction in some aspects of lung function. The authors expressed the opinion that this effect had little clinical relevance and was likely a reaction to large amounts of dust, but not specifically to paper dust.

Thoren et al. (1989) replicated the work of Jarvholm et al. (1988) at another mill where average paper dust exposures among the mill workers were less than 5 mg/m^3. Thoren et al. reported no effects on lung function among workers exposed to paper dust. They did, however, find that mill workers with exposures to paper dust reported more nasal congestion, throat irritation, and cough with phlegm than did office workers.

It is not clear that the effects of exposure to high levels of paper dust reported in these studies can or should be equated to effects that might be associated with exposure to high levels of cellulose. Thoren et al. (1989) reported that up to 25% of the weight of "paper dust" was in fact inorganic (not cellulose) and that both fibres and particles were present. Most of the particles contained aluminium and silica and likely came from clay used as a filler in the paper. Similarly, both Ericsson et al. (1988) and Jarvholm et al. (1988) noted that various additives were present in the paper dust, although at low levels.

More recently, Kraus et al. (2004) studied lung function among workers in tissue producing factories in Germany that, unlike the facilities studied in Sweden, did not use any recycled materials in their furnish. They reported quite high exposure levels, with an average ambient inhalable dust level, following 148 measurements, of 12.4 mg/m^3. The highest concentration of inhalable dust measured around paper machines during regular production was 30 mg/m^3 and during cleaning of equipment with pressurized air, a high of 96 mg/m^3 was reported. In order to express various workers' exposures in a common metric, years of work and dust levels of work locations were used to calculate an exposure index of "dust-years." The authors reported that a "restrictive pattern of lung function impairment occurs with increasing cumulative exposure to soft tissue paper dust." They also noted that exposures in their study were very high and speculated that lung overload could be an important factor in the loss of lung function seen in the study. And, similar to Jarvholm et al. (1988), Kraus et al. concluded that the effects seen in their study were "unspecific due to the high dust concentrations, regardless of its fibre content," (i.e. related more to the quantity of dust than to the cellulose content of that dust).

Paper Manufacturing and Converting Workplace Exposures

Samples of airborne particulate matter were collected around a wide variety of paper machines and converting operations in order to characterize the nature of the cellulose found in that particulate matter (NCASI, 2004). Microscopic analyses revealed that much of the particulate matter collected was not cellulose. Using electron microscopy, it was determined that the percentage of particles and fibres identified as cellulose ranged from 5 to 75%, with an average of 27%. The bulk of the particulate matter collected in this study was non-fibrous. Further, much of the cellulose in the samples was present as nonfibrous fragments of cellulose fibres. In general, greater than 90% of the collected particulate matter was less than 10 µm in diameter and about 80% of the fibres were 10µm in diameter or less.

Studies Using Cellulose Insulation

Muhle et al. (1997) conducted a study using both "chemical[ly] pure microcrystalline wood cellulose fibres" and Isofloc, a recycled newspaper thermal insulating product treated with 12% borax and 8% boric acid. This study is described below under both "Laboratory Studies of Cellulose Fibre Persistence" and "Studies Using Intratracheal Instillation of Cellulose Fibres."

Hadley et al. (1998) purchased cellulose insulation (CI) (typically recycled newspaper with 15-20% fire retardant chemicals) and ground it to generate a particulate of which 35-40% was potentially respirable for rats. Rats were exposed to this dust for 6 hours/day, 5 days/week for a total of 21 exposures at levels of 0, 100, 500, or 2000 mg/m^3. The researchers reported evidence of dose-related pulmonary changes characteristic of inflammation and initial stages of the development of fibrosis.

Morgan et al. (2004) discussed the findings of Hadley et al. (1998) and noted that the exposure conditions in the Hadley et al. study were not representative of workplace exposures. Morgan et al. noted that exposure to high concentrations of CI containing such a high percentage of respirable particles would be expected to result in lung burdens that inhibit lung clearance mechanisms and cause an inflammatory response.

In 2001, the National Institute for Occupational Safety and Health (NIOSH) released the results of a series of studies in which researchers collected information on health symptoms and administered pulmonary function tests to 23 workers engaged in the installation of CI in residential and commercial buildings (NIOSH, 2001). The most commonly reported symptom related to CI application was eye irritation, which began during exposure to CI and improved once the exposure ended. Cough and nasal symptoms that were reported were not temporally related to CI exposure and the symptom "morning phlegm production," which was the most commonly reported symptom, appeared to be related more to smoking than CI exposure. None of the workers showed indications of occupational asthma and while a few workers reported lower respiratory tract symptoms, those symptoms were classified as mild and infrequent.

Morgan et al. (2002) isolated respirable particulate matter samples from a commercially available CI product. Respirable CI particles, composed mostly of fire retardant chemicals, were administered to rats by intratracheal instillation at a dose of 5 mg CI/kg body weight. For comparison purposes, another group of rats receive intratracheal instillations of 5 mg/kg titanium dioxide (TiO_2), which is a relatively nontoxic inert compound often used as a negative control in particulate toxicity studies. At 1, 3, 7, 14, and 28 days after instillation, bronchoalveolar lavage (BAL) was carried out on 5 animals/treatment group. At 14 and 28 days after instillation, lung tissues from 5 animals/treatment group were examined microscopically. Analysis of BAL fluid showed evidence of inflammation in rats treated with either CI or TiO_2 on days 1, 3, and/or 7 post-treatment, depending on the parameter measured, although by post-treatment day 14, all measurements had returned to normal. On day 28 post-treatment, levels of an amino acid indicative of increasing deposition of collagen were elevated in BAL fluid of CI-treated rats. Microscopic examination of lung tissue from CI-treated rats showed a granulomatous lung inflammation that was mild to moderate in severity, persistent, but non-progressing over the course of the study. There was collagen present in the granulomatous nodules, but no evidence of pulmonary fibrosis. The lungs of TiO_2-treated rats contained scattered accumulations of macrophages with no accumulation of collagen at both days 14 and 28 post-treatment. The authors concluded that the acute pulmonary toxicity of respirable CI particles was not significantly different from that of TiO_2, but noted that the potential chronic toxicity of CI particulate matter had yet to be investigated.

Cellulose Insulation Applicators Exposures

NIOSH carried out exposure assessments among contractors applying cellulose insulation in residential and commercial buildings (NIOSH, 2001). They found that respirable dust levels were typically low during all CI operations, but total dust exposures have the potential to exceed the

OSHA limit of 15 mg/m^3 total dust. Similar to the findings of the NCASI study, NIOSH found that CI dust contained mostly particles, not fibres. NIOSH also reported that most of the fibres were large and would not travel into the lower areas of the lung.

Laboratory Studies of Cellulose Fibre Persistence

The persistence of fibres within the lung is one of the key factors that influence whether or not a fibrous substance will induce inflammation, leading perhaps to fibrosis, or initiate a carcinogenic response. Several researchers have studied the biopersistence of cellulose fibres in the respiratory tract of laboratory rats. There are two commonly used methods for introducing fibres into the respiratory tract for research purposes. Both generally start with the isolation of respirable fibres, or, sometimes, more specifically, WHO fibres from the test material. The most realistic method for exposing test animals to fibres is through inhalation. In this approach, the researcher generates a uniform suspension of fibres in air and the test animals are exposed to that atmosphere, thus inhaling the fibres. Unfortunately, this approach is typically costly. In addition, fibres and large particles are complicated to work with because they tend to "fall out" of the air, making it difficult to maintain homogeneous exposure atmospheres or the desired exposure concentrations. This leads many researchers to resort to intratracheal instillation, a process in which fibres are suspended in a saline solution, the test animals are sedated, and aliquots of the fibre suspension are deposited directly into the trachea. Intratracheal instillation, of course, has its own drawbacks, including that the distribution of the dose to respiratory tissues is highly artificial and that it may generate a series of macrophage reactions that do not accurately reflect the events that occur following inhalation exposure (Kennedy and Valentine, 1994).

Muhle et al. (1997) used "chemical[ly] pure microcrystalline wood cellulose fibres" and Isofloc, a recycled newspaper thermal insulating product treated with 12% borax and 8% boric acid. Respirable fibres were isolated and administered to 10-week-old female rats by intratracheal instillation. The authors noted that sufficient fibre mass was instilled to overcome normal macrophage-mediated particle clearance, thus generating lung particle overload conditions. The purpose of choosing to overload the lungs was to inhibit macrophage-mediated clearance in order to determine whether there would be any enzymatic digestion of the fibres in the lungs. Test animals were sacrificed at 2 days and 1, 3, 6, and 12 months after treatment. The researchers found that both purified cellulose fibres and Isofloc fibres were highly persistent, indicating that little to no enzymatic digestion of cellulose took place during the course of the study. Interestingly, the researchers reported that after about 6 months, the Isofloc fibres began splitting into thinner fibrils and branching. The significance, if any, of this splitting and branching is unknown.

Warheit et al. (1998) exposed male rats via inhalation to a 575 fibre/cc aerosol of Thermocell mechanical wood pulp, which was described as a high-purity cellulose material, for two weeks. At the end of the exposure period, lung burdens were in the range of 3×10^7 fibres. Clearance of fibres was moderate to slow, declining from an average of 2.84×10^7 fibres in the lung to 1.55×10^7 fibres over the course of three months.

Warheit et al. (2001) studied the mechanisms of biodegradability of cellulose fibres from Thermocell mechanical wood pulp, a high-purity cellulose material. Like Muhle et al. (1997), these researchers found no evidence that cellulose fibres are likely to be degraded through the actions of enzymes found in lung fluids.

Studies of In Vitro Toxicity of Cellulose Fibres

In *in vitro* toxicity testing, isolated cells or tissues are exposed to cellulose fibres. Adamis et al. (1997) isolated macrophages from the peritoneal cavity of male rats and incubated the cells for 3 hours with a suspension of cellulose fibres made from a cellulose product used for thin-layer chromatography (no further details on cellulose source provided). At the end of the incubation period, the fluid in which the macrophages were incubated was analyzed for the presence of lactate dehydrogenase (LDH), an enzyme that is released when cells are damaged. There was no evidence of LDH release, indicating that the cellulose fibres did not cause injury to peritoneal macrophages under the conditions of this study.

Cullen et al. (2002) used rat alveolar macrophages and the lung epithelial cell line A549 in monolayer cell cultures to study the cellular toxicity of cellulose fibres derived from a thermomechanical wood pulp. WHO fibres were isolated, added to cell cultures in 96-well plates, and incubated for 18 hours. At the end of the incubation period, little to no LDH was released from alveolar macrophages at any of the 3 fibre levels used. At the lowest fibre level, 6 x 10^5 fibres/well, LDH release from A549 cells was not much different from that of untreated control cells. At the highest fibre level, 600 x 10^5 fibres/well, LDH release was about twice that observed in controls, but was still quite low. The authors concluded that cellulose fibres have low intrinsic toxicity.

Studies of Intraperitoneal Injection of Cellulose Fibres

In intraperitoneal (IP) injection, cellulose fibres are injected directly into the peritoneal cavity of laboratory animals. The suitability of IP injection as a route of administration of fibres has been questioned by many. Cullen et al. (2002), while they used IP injection, acknowledged those concerns:

> The i.p. injection test has been heavily criticized because of the unnatural route of administration of fibres (the peritoneal cavity rather than the lung) and the large doses of fibre injected. However, the assay has been used to test many fibre types and is part of the European fibre testing protocols.

In the study described by Cullen et al. (2002), WHO fibres were isolated from thermomechanical wood pulp said to be of high purity and then injected into the peritoneal cavities of rats at levels of 10^6, 10^7, 10^8, or 10^9 fibres/animal. The mass of cellulose associated with the highest dose level was 116 mg. The rats were observed over the course of their lifetime for the development of tumours. Upon autopsy, there were widespread adhesions and large granulomas in the peritoneal cavities of animals receiving the highest dose of cellulose and cellulose fibres could be seen in the lesions. No granulomas or adhesions were seen in the two lower dose groups while the 10^8 fibre group had smaller granulomas and only slight adhesions. At the 10^9 fibre dose, 9 of the 49 rats had sarcomas. One of 48 rats and 1 of 50 rats had mesotheliomas in the 10^8 fibre and 10^7 fibre dose groups, respectively. One of 50 rats in the 10^6 fibre dose group had an angiosarcoma.

In another study carried out by Cullen and colleagues, respirable cellulose fibres were isolated from a high-purity thermally processed wood pulp (Cullen et al., 2000). Juvenile male mice received IP injections of 10^4, 10^5, 10^6, 10^7, or 10^8 fibres per animal in 0.5 ml of saline. A mass of 11.6 mg was required to obtain 10^8 fibres. Test animals were sacrificed one, 3, and 7 days after cellulose administration and the numbers of inflammatory cells present in the peritoneal cavities were determined. For all but the lowest dose, numbers of inflammatory cells were increased on day one post-treatment, but had returned to normal by day 7 post-treatment.

Studies Using Intratracheal Instillation of Cellulose Fibres

Milton et al. (1990) isolated respirable fibres from microgranular cellulose, a purified cellulose product manufactured from cotton fibre and used as a thin-layer chromatography adsorbent. Male Golden Syrian hamsters were dosed twice a week for 6 weeks via intratracheal instillation with 0.75 mg cellulose per 100 grams of body weight. Animals were sacrificed 8 weeks after the last instillation. Cellulose treatment was associated with decreased lung distensibility, granulomas in the lungs, and increased density of parenchymal tissue, all of which indicate the development of lung fibrosis. The researchers noted that the final lung burden of cellulose in this study, 3 mg/g lung tissue, may have led to lung particle overload.

Tatrai and Ungvary (1992) instilled a single 15 mg dose of cellulose suspended in 1 ml of saline solution into male rats. Cellulose fibres were prepared from a purified cellulose product used as a thin-layer chromatography adsorbent. Animals were sacrificed one or 3 months after treatment. Cellulose treatment was associated with the development of a chronic inflammatory foreign body granulation with mild to moderate fibrosis in the bronchiolar and alveolar regions of the lung.

Adamis et al. (1997) generated cellulose fibres from a purified cellulose product used in thin-layer chromatography. Male rats received a single dose of 15 mg per animal and animals were sacrificed on days 1, 3, 7, and 30 post-treatment for BAL and histological examination of the lungs and regional lymph nodes. On days 1 and 3 post-treatment, indicators of cytotoxicity were present in BAL fluid, but by day 7 post-treatment, there was no longer any difference between treated and control animals. Histological examination revealed the onset of inflammation 1 day post-treatment and indicators of the development of fibrosis began to appear by day 7 post-treatment. The authors noted that phagocytosed cellulose fibres could seen inside giant cells in the interstitium and the alveoli one week after treatment and one month after treatment granulation composed of foreign body-type giant cells was evident.

As described above in studies on cellulose fibre persistence, Muhle et al. (1997) isolated respirable cellulose fibres from "chemical[ly] pure microcrystalline wood cellulose fibres" and Isofloc, a recycled newspaper thermal insulating product treated with 12% borax and 8% boric acid. Fibres were administered to 10-week-old female rats by intratracheal instillation. The authors noted that sufficient fibre mass was instilled to overcome normal macrophage-mediated particle clearance, thus generating lung particle overload conditions. Test animals were sacrificed at 2 days and 1, 3, 6, and 12 months after treatment. At 2 and 30 days after treatment, both cellulose and Isofloc-treated rats had "mild multifocal granulomatous inflammation" of the lungs. Cellulose fibres were present inside alveolar macrophages. After 3 and 6 months, indications of developing lung fibrosis were present and at one year post-treatment, the severity of lesions was increased.

Studies of Inhalation Exposures to Cellulose Fibres

As a part of the study of cellulose fibre persistence described above, Warheit et al. (1998) exposed male rats via inhalation for 2 weeks to 300 or 575 fibre/cc aerosols of Thermocell mechanical wood pulp, which was described as a high-purity cellulose material. At the end of the exposure period, lung burdens in the high dose group were in the range of 3×10^7 fibres per animal. The lungs of the rats were evaluated immediately after the final day of exposure, 3 and 10 days, and 1 and 3 months later through BAL and histology. BAL analysis revealed indications of a mild and transient pulmonary inflammation which had returned to control levels within 10 days post-exposure. Histology revealed a minimal alveolar macrophage accumulation at sites of fibre deposition which persisted through the 3-month post-exposure sacrifice. The authors

concluded that the inhalation of cellulose fibres at the dose levels used in this study did not produce sustained pulmonary inflammation.

Cullen et al. (2000, 2002) generated test atmospheres of cellulose dust from a high-purity thermally processed wood pulp. Rats were exposed to a concentration calculated to yield exposures of 1000 WHO fibres/cc for 7 hours/day for 1, 3, 8, or 14 days of actual exposure over a 3-week period. Animals were sacrificed 18 hours after the completion of each exposure period with the exception of one group that was maintained for a period of 28 days without further exposure. BAL fluid was collected and analyzed for the presence of inflammatory cells at every sacrifice point. Histopathological examination of the lungs was conducted following 14 days of exposure and at the 28-day recovery point. The number of inflammatory cells present in BAL fluid was increased following 1 and 3 days of exposure, but by the end of 14 days of exposure, levels had returned to nearly normal and were equal to those of control rats by the end of the 28-day recovery period. Microscopic examination of lung tissue revealed that immediately following 14 days of exposure, aggregates of macrophages and other inflammatory cells were present at branch points of the bronchioles and inside the interstitium. At the end of the 28-day recovery period, the numbers of cells in these aggregations appeared to be reduced, both in the bronchioles and the interstitium. The authors calculated the expected lung burden following 14 days of exposure and noted that lung particle overload conditions likely existed. They also observed that while the lung lesions observed in this study are similar to those observed in previous intratracheal instillation studies using cellulose fibres, they were also similar to those observed after exposures to nonfibrous low-toxicity dusts sufficient to produce lung overload conditions. The authors concluded that the cellulose dust used in their study could produce an acute, but resolving, inflammatory response, which suggests that it is of relatively low toxicity.

Health Effects Research Summary

Laboratory research using purified cellulose fibres or cellulose containing-dusts demonstrates that under some circumstances, cellulose *can* produce tumours, inflammation, and fibrosis in the peritoneal cavity or lung, depending on how it was administered. Unfortunately, these studies were nearly universally carried out using either methods of exposure that are irrelevant to real-world conditions or exposures that are orders of magnitude above those likely to be experienced by production workers or end-users of paper products. This means that while it can be said that exposure to cellulose *could* have adverse effects, it cannot be said that exposure to cellulose *will* have adverse health effects or even that it is *likely* to do so.

Further, as pointed out by Cullen et al. (2000), some of the results of existing research produce an interesting paradox. It has been generally accepted that fibres persisting in lung tissue initiate a cascade of events that lead to increasing inflammation and resultant development of fibrosis. The work of Muhle et al. (1997) and Warheit et al. (1998, 2001) indicate that cellulose fibres are persistent in the lungs, yet studies by Cullen et al. (2000, 2002) and Warheit et al. (1998) indicate that even if cellulose exposure is associated with initial inflammatory responses, such inflammation resolves fairly quickly, even in the face of continued exposure, which is entirely unexpected and requires additional research in order to understand.

Studies of paper mill workers in Sweden and Germany provide equivocal evidence of adverse effects on lung function and symptoms of upper respiratory tract irritation among workers exposed to high levels of dust in paper mills producing tissue and related products. It is not clear, however, whether this is related to any property specific to cellulose or is simply a function of high exposures to an inert, insoluble substance. The researchers involved appeared to believe the latter, stating that the likelihood was that the effects were nonspecific in nature.

Research on cellulose insulation does not appear to be particularly relevant to concerns about the toxicity of cellulose. Studies have shown that most of the cellulose in CI is not small enough to be inhaled and the bulk of the respirable dust generated during CI installation is from fire retardant chemicals.

Recent Regulatory History of Cellulose

Both the United States Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH) have developed occupational exposure limits (OELs) for cellulose. The ACGIH Threshold Limit Value (TLV) for cellulose is 10 mg/m^3 total dust (8-hr TWA). The OSHA Permissible Exposure Limit (PEL) for cellulose is 15 mg/m^3 total dust and 5 mg/m^3 respirable dust (both 8-hr TWAs). Both entities have historically considered cellulose to be biologically inert and nontoxic.

In recent years, cellulose has received attention as a potential substitute for inorganic (asbestos) and man-made-vitreous (fibreglass) fibres. This, coupled with greater understanding of the fact that some of the physiological effects of inorganic fibres seem to be associated with the physical, rather than chemical, qualities of those fibres, has led to greater interest on the part of regulatory agencies in the potential health effects of cellulose fibres, and in particular, the potential carcinogenicity of those fibres.

In July, 1994, cellulose insulation was nominated (purportedly by a representative of the fibreglass industry) to the US National Toxicology Program (NTP) for in-depth toxicity testing. As a part of the response to this nomination, NIOSH conducted an analytical characterization of cellulose insulation and an exposure assessment of contractors applying CI in residential and commercial buildings. In addition, a 28-day intratracheal instillation study using rats was carried out by NTP. The results of these studies are described in previous sections of this report.

In November, 1998, the United Kingdom Department of Health's Committee on Carcinogenicity of Chemicals in Food, Consumer Products, and the Environment was asked by the Health and Safety Executive (HSE) to provide advice on the relative carcinogenic risks of three chrysotile asbestos-substitutes: polyvinyl alcohol (PVA), p-aramid, and cellulose fibres. Specifically, they were asked whether those three materials posed less of a carcinogenic risk than chrysotile with respect to occupational and consumer health. While the committee's review did not reach any specific conclusions with respect to the carcinogenicity of cellulose fibres, they did conclude that the respirable fraction of cellulose fibres in workplace atmospheres appears likely to be very small and that any carcinogenic risk posed by cellulose is likely to be less than that posed by chrysotile asbestos.

In December, 2002, the European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) issued an "Opinion on Risk to Human Health From Chrysotile Asbestos and Organic Substitutes," in which they considered the scientific evidence currently available on the issue of whether or not cellulose, polyvinyl alcohol (PVA), or p-aramid fibres posed an equal or greater risk to human health than chrysotile asbestos. They concluded that these potential substitutes were indeed less harmful than chrysotile asbestos, but emphasized that workplace controls to limit exposures to these substitute fibres should not be relaxed. They also strongly recommended additional research on the toxicity of substitute fibres.

In February, 2003, the 6th Advisory Group of the International Agency for Cancer Research (IARC) Monographs assigned a high priority to an evaluation of the potential carcinogenicity of

organic fibres, including cellulose fibres. This assignment will not result in the undertaking of research by IARC, but rather may lead to the formation of an expert panel to evaluate all of the available evidence on the potential carcinogenicity of the specified organic fibres. Unfortunately, IARC reviews often consider only whether a particular substance *can* be carcinogenic, not whether it is likely to be so in "real life." An IARC finding that cellulose fibres are carcinogenic is likely to have at least some ramifications for paper producers since it may lead to reductions in OELs and additional product labelling and notification requirements.

Although the issue of cellulose and modified cellulose products in pharmaceuticals, food products and similar consumer goods has been addressed in the past by Health Canada, we are not aware of any recent formal Health Canada activities addressing issues related to inhalation exposure to cellulose fibres.

Conclusions

Available evidence suggests that cellulose is indeed a reasonably inert substance with low intrinsic toxicity. It does not, however, appear to degrade once deposited inside the respiratory tract, meaning that the only means for the body to rid itself of inhaled cellulose particles or fibres is through the activity of alveolar macrophages or similar clearance mechanisms that can physically remove particulate matter from the respiratory tract. These clearance mechanisms can be seriously impaired by the deposition of large quantities of particulate matter, making it critical to keep worker exposures below the levels at which lung particle overload is likely to occur.

Whether or not cellulose fibres are carcinogenic has been of some concern among various regulatory agencies. There is no evidence that inhalation exposures to cellulose dust result in the development of lung cancer of any type, but this area of research is by no means well developed. There have been no long-term inhalation studies at all and most of the short-term inhalation studies that have been conducted have used unrealistically high doses. Further, most of the studies that have been conducted using cellulose fibres have used routes of exposure that bear little resemblance to reality, leaving their relevance open to discussion.

On the regulatory front, the impending IARC evaluation probably has the greatest potential to impact manufacturers of paper products. If IARC determines that cellulose fibres should be considered carcinogenic or likely to be carcinogenic in humans, that decision would likely set into motion reviews by various governmental health and safety agencies, possibly resulting in stricter workplace exposure limits and more demanding product stewardship requirements.

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Glossary

Alveolar macrophage – vigorously phagocytic macrophage on the epithelial surface of lung alveoli where it ingests inhaled particulate matter

Alveolar – relating to an alveolus

Alveolus/Alveoli – in the lungs, terminal dilations of the bronchioles where gas exchange is thought to occur

Angiosarcoma – rare malignant neoplasm believed to originate from the endothelial cells of blood vessels

Asbestosis – lung disease caused by asbestos, characterized by fibrosis in the alveolar walls and the presence of asbestos fibres, either free or coated with a proteinaceous material (asbestos bodies)

BAL – see bronchoalveolar lavage

Bronchoalveolar lavage (BAL) – procedure during which a distal airway is blocked and liquid is then introduced into the airway and recovered for examination of cell types and microorganisms

Chronic – in the context of toxicity studies, exposures that occur over a long period of time

Fibres – particles that have a length-to-width ratio of at least 3:1

Fibrosis – formation of fibrous tissue as a reparative or reactive process

Giant cells - an unusually large cell; especially a large multinucleate phagocytic cell

Granulation – a granular mass in or on the surface of any organ or membrane

Granulomas – nodular inflammatory lesions, usually small or granular, firm, persistent, and containing compactly grouped mononuclear phagocytes

Interstitium – a small area, space, or gap in the substance of an organ or tissue, also connective tissue

Macrophage – large amoeboid mononuclear phagocytic cell

Malignant Mesothelioma – a tumour of the cells covering the surface of the visceral and parietal pleura (the membrane lining the chest cavity)

Mucociliary escalator – the mucous layer covering the tracheobronchial segment of the respiratory tract is moved upwards by the beating of underlying cilia; this transports deposited particles and particle-laden macrophages upward to the oropharynx where they are swallowed and pass through the digestive tract

Respirable fibres – fibres small enough to penetrate into the lower segments of the respiratory tract, the precise diameter of which varies depending on the species of interest; rat-respirable fibres are generally defined as less than 3 µm in diameter

Sarcomas – a connective tissue neoplasm, usually highly malignant, formed by proliferation of mesodermal cells

WHO fibres – rat-respirable fibres defined by the World Health Organization as being less than 3 µm in diameter, more than 5 µm in length, and with an aspect ratio (length:width) of at least 3:1

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