Pharmaceuticals Manufacturing:

What do we know about the occupational health and safety hazards for women working in the industry?[1]

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March, 2009

[1] This is an abridged version of "Occupational health and safety hazards in pharmaceuticals manufacturing: Past, present and future knowledge, policies and possibilities, particularly for women," written by Dorothy Wigmore for Women and Health Protection.

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1. Introduction

> *Little is known about the health risks of working in the pharmaceutical industry. On the surface, the industry looks clean. The production of medicinals demands a carefully maintained and sterile working environment and the white lab coats worn by workers add to the illusion* (Turshen, 1978).

The pharmaceutical industry has been described as dynamic and growing, in terms of sales, number of employees, and GDP (Health Canada, 2006; LeClerc, 2002). The Canadian government considers biopharmaceuticals to be an important innovation leader (Industry Canada, 2008b). It is an industry in which companies, government regulators and researchers focus on the "safety" of the products and their effects on end users and the environment (Ågerstrand, Rudén & Wester, 2008; Batt, 2004; Canadian Environmental Law Association & Lowell Center for Sustainable Production, 2009). However, the continuum of exposures to pharmaceutical ingredients—from development and manufacturing, through marketing and consumption, to our waterways—also includes the workplace. Unfortunately, this key aspect of the life cycle of products in this sector is a poor cousin to other issues.

Occupational health and safety (OHS) falls under the broad umbrella of public health (Levy & Wegman, 2000). In 1950, the World Health Organisation (WHO) and the International Labour Organisation (ILO) declared that the goals of occupational health should be to:

- promote and maintain the highest degree of physical, mental and social well-being of workers,
- prevent ill-health among workers caused by their working conditions,
- protect workers from factors adverse to their health in their employment, and
- place and maintain workers in occupational environments adapted to their individual physiological and psychological conditions.

While more is known now than when Turshen wrote the statement quoted above in 1978, there still is much to learn about OHS hazards in the pharmaceutical sector. Gender-related issues are particularly important, since women comprise more than half of the pharmaceutical research, development, and production workforce in Canada. Women have different biological responses to some hazards, are different from men in their shapes and sizes (whatever their heritage) and typically are exposed to different hazards than male co-workers.

This paper describes how pharmaceuticals are developed and produced, and what is known about the associated hazards. It includes an overview of health and safety laws in Canada and elsewhere, as well as some examples of relevant best practices. We conclude with a series of recommendations.

2. The pharmaceutical industry

2.1 The labour force

The pharmaceutical manufacturing industry produces therapeutic substance—human and veterinary medicines, drugs, and related products—in an increasingly concentrated set of mostly transnational conglomerates and sub-contracting facilities. The sector has five broad areas of

activity: research and development (R&D), manufacturing, sales and marketing, distribution, and administration.

In Canada, about 24,000 people worked in the pharmaceutical industry in 2001, up 22 percent in five years (Leclerc, 2002).[2] By 2006, the census counted 29,715 people employed in the sector—15,880 women and 13,835 men. The jobs are concentrated in Quebec and Ontario, with small enclaves in British Columbia, Manitoba, and Nova Scotia (Statistics Canada, 2008). In the 1996 census, the major pharmaceutical industry occupations were: technical sales specialists, wholesale trade (12%); chemists (6%); chemical plant machine operators (5%); and applied chemical technologists and technicians (5%). Women made up 73 percent of the business, finance and administrative occupations and 56 percent of occupations unique to processing, manufacturing and utilities (Human Resources and Skills Development Canada, 2007).

Table 1 -- Number of establishments in Canada by employment size category and region Pharmaceutical and Medicine Manufacturing
(NAICS 32541) -- June 2008
(Statistics Canada, 2008, as cited by Industry Canada, 2008c)

Province or Territory	Employment Size Category (Number of employees)			
	Micro 1-4	Small 5-99	Medium 100-499	Large 500+
Alberta	8	5	1	0
British Columbia	20	18	3	0
Manitoba	1	1	3	2
Newfoundland and Labrador	1	1	0	0
Nova Scotia	1	8	1	0
Ontario	36	61	22	3
Prince Edward Island	2	2	1	0
Quebec	23	45	15	2
Saskatchewan	0	1	0	0
Canada	92	142	46	7
Percentage distribution	32.1%	49.5%	16.0%	2.4%

Data from 1999 indicated that sector employees worked an average of 39 hours weekly (two hours above the norm), had 8.5 weekly overtime hours compared to 9.2 for all industries, and were almost all full-time (part-time workers were 5 percent versus 19 percent for the whole economy) (HRSDC, 2007). Only 10 percent of the workforce was unionised in 1999, compared to a national rate of 31 percent (HRSDC, 2007). In the U.S., only five percent of the drug manufacturing workforce is unionised. This is less than half the rate in other manufacturing jobs (U.S. Bureau of Labor Statistics, 2007). In 2006, average wages in drug manufacturing facilities were $47,473 for production employees and $72,165 for administrative employees (Industry Canada, 2008b).

Table 1 shows that in 2008, most establishments in Canada (usually individual workplaces) were in the micro, small or medium categories for number of employees (Statistics Canada, 2008 as

[2] The actual numbers employed by pharmaceutical companies are difficult to determine. R&D employees working outside a pharmaceutical plant are covered by a different NAICS code than those working at a manufacturing site. The research-based pharmaceutical company organisation—Rx&D—said in 2004 that about 24,000 people worked for 50-plus companies, including about 4,000 doing R&D; the industry supports another 6,000 at universities, hospitals and research institutions (CanadaPharma, 2004). The Canadian Generic Pharmaceutical Association says more than 11,000, in total, work for their member companies at the time of writing (Canadian Generic Pharmaceutical Association, 2009).

cited in Industry Canada, 2008a). Multinationals dominate the general market while smaller firms usually work in a specialized niche (Leclerc, 2002). Female-male breakdown is not reported.

2.2 The processes

There are three basic steps in making drugs: research and development (R&D), followed by primary (bulk or active ingredient) production and secondary (dosage form) manufacturing (Environmental Protection Agency, 1997). Each has parallel work activities elsewhere. Research is much like (other) academic research laboratory work, while development is similar to small-scale chemical production; the latter is different in that animal and human testing of the active ingredient is required. The manufacturing processes are essentially large-scale chemical production with lots of batches (unlike most chemicals) and special regulatory oversight focused on the "safety" of the end product. (Biologics and vaccines follow a slightly-different path.)

Unlike other consumer goods, pharmaceutical products are intended to improve health by effecting changes in the body without unacceptable harmful effects. In many ways, their production resembles pesticide manufacturing. An active ingredient is the focus of each product, whether its concentration is .01 or 10 percent. Intermediates[3] and a wide variety of toxic substances are common to both. Pesticides have their "inerts". Pharmaceuticals have their excipients and "pharmaceutical necessities". The former are inert ingredients needed to help produce the type of product (e.g., tablet, capsule, liquid) and "may affect the rate of absorption, dissolution, metabolism and distribution in humans or animals" (Tait, 1998, p.79.3). The latter are binders, fillers, flavouring and bulking agents, preservatives, and antioxidants; they can be emulsifiers, suspending agents, ointments, "pharmaceutical solvents", and excipients (Tait, 1998).

For both drugs and pesticides, manufacturers, researchers, and regulators tend to focus only on the active ingredient, to the exclusion of other substances involved in the research or production process. Health and safety studies and reports usually deal with individual substances or hazards, rather than on how they might interact to cause adverse effects. Therefore, it is helpful to describe the main pharmaceutical production steps and the hazards that may be present in each one.

The R&D step in the process may last for many years with no guarantee that the product will get beyond the pilot manufacturing stage. The work can be done in the lab of a manufacturing facility, university or independent facility. Scientists and technicians may use computer simulation, combinatorial chemistry, and high through-put screening to speed up and simplify finding new substances or adapting old ones (BLS, 2007).

Once they "find" a new chemical entity (NCE)—also known as an active pharmaceutical ingredient or API—it is screened using *in vitro* (bacterial culture) and *in vivo* (animal) tests. The type of test depends on the product's development stage; basically it is designed to obtain information about general and specific acute and chronic toxic properties, such as genotoxicity, irritation, sensitisation, and carcinogenicity (BLS, 2007; Olson, Binks, Newton, & Clark, 1997;

[3] An intermediate is a material produced during a manufacturing process that must undergo further molecular change or processing before it becomes a bulk pharmaceutical substance.

Stave & Joines, 1997). Only substances that pass these tests (said to be one in every 5,000 to 10,000 screened compounds) are tested on people in three sets of trials; Health Canada must approve any human testing. Synthesis of the substance may require a pilot manufacturing facility, with new processes, specialised equipment, and measures to prevent worker exposure to hazards (or to keep exposure at an "acceptable" level). More and more, this work seems to be (sub-) contracted out, particularly for high potency drugs (Guest & Newton, 1997). Health Canada must review the trial results and give approval before commercial production starts. There are similar provisions in other countries.

Once approved, bulk quantities of new APIs or NCEs are made by synthesis and purification processes. (It should be noted that very few of these active ingredients are made in Canada.) Sometimes called "basic production", the specifics depend on the product:

- **fermentation** (e.g., antibiotics, steroids and vitamins), further divided into three steps—inoculum and seed preparation, fermentation, and product recovery or isolation;
- **organic chemical synthesis** (e.g., newer drugs) in which a "mother liquor" is put through separation, purification, and filtration processes in "campaigns" or short bursts of intensive activity; or
- **biological and natural extraction** of plant or animal matter in campaigns lasting a few weeks (Tait, 1998).

Fermentation involves starting with a biological culture, filtration, solvent extraction and recovery, other purification procedures, drying, formulation and packaging. Equipment includes high-pressure vessels, centrifuges, drying trays, and solvent and effluent treatment. Synthesis uses multi-purpose and multi-step reactors (reinforced pressure vessels) connected to other equipment and supplies, along with instruments to measure temperature, pressure and weight and control the process. A series of chemical reactions produce a finished product that usually is dried, milled, and blended. Extraction processes use solvents to remove fats and oils from the starter material(s). Metal compounds often are used to precipitate (remove) the substance of interest and phenols disinfect during the process (Tait, 1998).

Whatever the process, most drugs are made in a "batch" method

> (in which) a particular substance or "intermediate" is manufactured in a "campaign" for periods ranging from a few days to several months until sufficient material is manufactured to satisfy the projected sales demand. At the end of the manufacturing campaign, another pharmaceutical intermediate or substance is made. The same equipment with potentially different configurations and the same operating personnel are often used to make a different intermediate or substance, utilizing different raw materials, executing different processes, and generating different waste streams (EPA, 1997).

Equipment that is used more than once must be cleaned, to avoid cross-contamination, using water, steam, detergents, and/or organic solvents. Cleaning validation guidelines set out the standards to be met (Health Canada, 2008; LeBlanc, 2008). Solvents used in bulk preparation are listed in Appendix 1, categorised by the process(es) in which they may be found. Many are carcinogens or produce other chronic effects.

Even though much is automated in these processes, worker tasks required include:

- weighing and dispensing solids (by hand-scooping) and liquids (using pumps or pouring),
- charging and discharging solids and liquids from containers and process equipment (when it's not done by gravity, pneumatic, or mechanical transfer),
- manual materials handling (of sometimes heavy containers, trays, etc.),
- equipment maintenance and repair, and
- watching controls and processes (Tait, 1998).

The environments can be noisy, hot, and humid. Surfaces can be hot and slippery; some may be covered with dust from the process. There are many moving machinery parts and pressurised pipes and vessels. Some work is done in confined spaces and/or with high-energy sources. Powders can explode. Solvents can burn and/or explode, especially in organic synthesis. General manufacturing practice and other quality control rules set by regulatory agencies, customers, and/or pharmaceutical organisations cover a number of these processes and the equipment used. Health and safety laws apply to all of them. (See section 5.)

Once the primary processes have been completed, the next step—secondary manufacturing—is to produce a finished product in the desired dosage form. The form may be an aerosol, capsules, creams, gels, injectables, lotions, ointments, powders, suppositories, syrups, or tablets (Burling & Shah, 1997). Exposure to hazards is most likely when making tablets and capsules. About 70 percent of all drugs are made into some type of tablet that must be a certain shape and size, stable, able to withstand deterioration/decomposition, and still able to dissolve in the stomach.

Common tablet production stages include:

- mixing excipients and pharmaceutical necessities with the active ingredient,
- granulation to increase particle size to improve fluidity and compressibility,
- wet or dry compression,
- direct dry compression using dibasic calcium phosphate and microcrystalline cellulose,
- wet granulation, in which the liquid is water and sometimes isopropanol, ethanol, or methanol, and
- tablet coating (Burling & Shah, 1997).

The processes and methods for other forms depend on the final product. Some must be able to penetrate the skin. Others can be in a liquid or powder (dust) state. A relatively new delivery system uses one of three types of liposomes. These are "microscopic spheres with an aqueous core surrounded by one or more lipid layers" (Burling & Shah, 1997, p. 38). The drug is attached to the lipid by layer or dissolved in the liquid core; it can be put into the liposome during the manufacturing process or later.

Nanoparticles also are making their way into pharmaceutical products (National Institute for Occupational Safety and Health, 2009; Royal Commission on Environmental Pollution, 2008). This allows the resulting drugs to be more specific in their targets within the body. Nanotechnologies refer to a variety of methods that use:

> the science of engineering on a molecular scale, in effect building matter atom-by-atom from the 'bottom up.' The prefix 'nano' denotes a fraction of one-one billionth, and nanotechnology

> involves the construction of matter a billionth of a meter in size: roughly the size of several atoms (International Center for Technology Assessment, 2009, para 1).

However they are made, final products are packaged—into small containers, blister packs, etc., and then into larger containers—and stored in a warehouse, before being sent for distribution.

2.3 Gender questions

There is little detailed information about the work women typically do in pharmaceutical plants and R&D facilities, making it difficult to analyse their roles and, hence, specific hazards they may encounter. The only clues found in a literature search come from a paper about the incidence of cancer in a Swedish plant. The researchers found that:

- women were 45 percent of those exposed to chemical, radiation, and "high risk" exposures in labs and production units;
- workers in pharmaceutical labs and production units were 60 percent female;
- 58 percent of the workers in biological labs were women; and
- 40 percent of those with indirect exposures from cleaning, washing, storage, and administrative work within labs and production facilities were female (Edling, Friis, Mikoczy, Hagmar & Lindors, 1995).

These distributions are consistent with the broad results in the 1996 Canadian census and provide a starting point to understand what work women do in this sector. They indicate that women working in pharmaceutical R&D and production facilities likely face most of the hazards discussed below. They are much less likely than men to be maintenance workers or to be operating heavy-duty materials handling equipment.

However, while the hazards facing women may be similar to those facing men, the effects may be different. Women's exposures often are not the same as those of their male co-workers because of anthropometric (body size and shape) differences, resulting variances in ergonomic design hazard exposures, and the actual tasks they perform. Furthermore,

> women's work-related health problems and risks have been largely underestimated by decision-makers, doctors and researchers... (There is e)merging literature showing that there are gender and ethnicity differences within job titles and work tasks that can modify exposure to risks, the nature of health problems, the impact of health problems and recourse in the event of a work-related accident or disease (Premji, Lippel & Messing, 2008, p. 16).

3. Hazards

3.1 Introduction

Pharmaceutical workers face a broad spectrum of workplace hazards, which can be categorised as follows:

- chemical and mineral (e.g., dusts, gases, vapours, solids, mists);
- physical (e.g., lighting, temperatures, humidity, radiation, electricity, noise);
- ergonomic design (repetition, force, awkward and static posture, environmental factors/physical hazards and stressors);
- safety and mechanical (e.g., poor maintenance/housekeeping, moving gears and parts on equipment);

- biological and communicable (e.g., viruses, bacteria, blood-borne pathogens, moulds); and
- work-related stressors (often framed by high physical and psychological demands, poor levels of support and respect, low control/latitude).

Knowledge of some drug-related hazards has been around a long time. Several contemporary authors reference the original occupational medicine specialist, Bernardino Ramazzini. In his 1713 book, *Diseases of Workers*, he wrote:

> Indeed, if we questioned closely those who work … in the shops of apothecaries … as to whether they have at time contracted some ailment while compounding remedies that would restore others to health, they would admit that they have very often been seriously affected (Ramazzini, as cited by Agius, 1989, p. 555).

In the 1940s, an Abbott Laboratories occupational physician described the relatively new organic synthesis of drugs: "(P)ractically no other single commercial enterprise presents such a wide variety of potentially toxic exposures or such a rapidly-changing advent of new chemical substances" (Watrous, 1947, p. 111). His review—which mentions female workers only twice—"provides a familiar list of headings and exposure issues to today's pharmaceutical occupational health practitioner" (Scott, 2003, p. 354).

Nevertheless, getting a handle on the hazards facing workers in pharmaceuticals work is a daunting task, especially from outside the industry. There are relatively few reports about the health effects of making specific NCEs and APIs, or pharmaceutical R&D and production in general. "Given the current scope of pharmaceutical manufacturing globally, the relative paucity of epidemiological studies is disturbing" researchers said 20 years ago (Teichman, Falming Fallon & Brandt-Rauf, 1988, p. 55). Fifteen years later, Scott (2003) reflects a similar theme: "well-known historical clusters" linked to particular classes of drugs dominate the literature and "there is a paucity of recently published data" (p. 354). Reviews about the reported health effects of pharmaceutical work are brief. A 2003 "in-depth review" by Heron and Pickering (employed by drug companies) is just over three pages, plus references. The 1998 effort by Teichman and colleagues (said to be authoritative) is three-and-a-half pages with references.

The dearth of information about pharmaceutical industry chemical hazards—particularly their long-term effects—is partly a result of the limited information about most chemicals on the market today. Few of the myriad of chemical and biological substances present in this sector have been studied for health effects, especially chronic ones. Heron and Pickering (2003) found reports about acute pharmacological effects—which they consider the most common harmful ones (for no stated reason)—were relatively rare. Exposure to steroid hormones and antineoplastic (sometimes called by the more generic term "cytotoxic") drugs dominated reports about chronic effects of potent compounds. They also report finding only six epidemiological studies about respiratory sensitisation and restricted airways and skin sensitisation. Nor is there much information about other hazards likely present in these jobs, particularly stressors and ergonomic design issues, even though they clearly are important; some of the largest companies describe both as the most common hazards in their facilities around the world (AstraZeneca 2008; GlaxoSmithKlein, 2008).

A further shortcoming in the limited data available is that the studies and reports do not seem to examine the most common type of establishments in Canada—those with small numbers of employees. The very low unionisation rate among North American pharmaceutical workers may be a factor in the dearth of information, as unions and their members have a history of raising health and safety issues, sometimes before OHS specialists are aware of a hazard.

It also may be significant that individuals employed by the industry dominate the relevant published literature. For example, they are all but two of 25 contributors to the 1997 pharmaceutical industry issue of the well-respected *Occupational Medicine. State of the Art Reviews*. Further, it is difficult to know how many authors were funded by companies or their representatives, or have worked for them. Only in the last few years have scientific journals required full disclosure of such connections. This raises questions about the biases that may be present, the stories that aren't told and the questions that are not being asked.[4]

Some OHS information can be gleaned from data about work-related injuries, diseases, and deaths. But access to industry-specific information about accepted compensation claims in Canada is difficult to obtain. The Association of Workers' Compensation Boards of Canada (AWCBC) collates information, but their expensive annual reports must be purchased, as do special data runs. More important, it is becoming clear that this source is unreliable and underestimates the true picture. Under-reporting is rampant in most countries. Canadian researchers found that 40 percent of all the claims that workers' compensation boards would have accepted[5] were never made (Shannon & Lowe, 2002). In the U.S., shoddy and poorly-enforced record-keeping complicates the under-reporting phenomenon (Whitmore, 2008). Around the world, the contribution of work environment to chronic diseases such as cancer is underestimated (Clapp, Howe, & Lefevre, 2005; Clapp, Jacobs, & Loechler, 2007).

Given the difficulties in finding reliable information about the spectrum of hazards in drug production and R&D work, the following discussion tries to give a flavour of what is available and to raise questions about hazards that likely are present. It starts with reports about the industry in general and then focuses on the chemical/mineral and biological/communicable categories, with special attention to reproductive/genotoxic hazards and carcinogens/mutagens. Safety, ergonomic design and stressors are covered in less detail.

3.2 Pharmaceutical industry studies and reports

General epidemiological studies of pharmaceutical industry workers have been done in Europe and the United States, but not Canada. The results include:

- a higher prevalence of hypertension and chronic bronchitis among long-term Serbian plant employees, and fewer capable of working (Milovanovic et al., 2007);

[4] Three recent American books are useful sources in this regard: David Michaels' *Doubt is their product*, Devra Davis' *The secret history of the war on cancer* and Markowitz and Rosner's *Deceit and denial: The deadly politics of industrial pollution*. Rick Rennie's *The Dirt* covers similar issues in a study of fluorspar mining in St. Lawrence, Newfoundland.

[5] Historically, compensation boards have been reluctant to accept claims for chronic effects (e.g. cancers), reproductive effects and musculoskeletal disorders, so under-reporting is likely higher for these kinds of illnesses and diseases.

- changes to the mouth and teeth in Polish sulphonamide workers, including leukoplakia (white, thick patches from epithelial hyper-keratosis, producing favourable conditions for development of cancer) (Nowicka, Zajaczkowska-Białowas, Kuc, & Sibora, 1988);
- in a mortality study of U.S. plant workers, higher suicide rates for males and females and questions about cancers (see below) (Thomas & Decoufle, 1979);
- "neither a clear relationship between occupational and mortality experience of pharmaceutical workers nor evidence of any excess in mortality risk" (p. 166) in a company study of people employed between 1950 and 1999 in a U.S. plant, although there were "slight not significant increases" (p. 165) in all-cancer standardised mortality ratios for production, lab and service workers (Dolan, Naumann, Sargent, Maier, & Dourson, 2005);
- possible occupational links to lymphatic-hematopoietic tissue cancer and non-Hodgkins' lymphoma among a smaller group of the same U.S. plant's (mostly male) workers, and lung cancer that could be work-related but was partially attributed to smoking, in a study that looked at anyone who had worked full-time between 1970 and 1996 and who had jobs with measured exposure to nine of the 50-plus chemicals known to have been in the plant (Marsh, Youk, Esmen, & Buchanich, 2005); and
- chronic and acute respiratory symptoms in a Croatian plant making a variety of unnamed drugs (Zuskin et al., 2004).

The multinational pharmaceutical companies generally provide health and safety information in reports and on their websites. For example, the 2007 *Corporate responsibility report* from GlaxoSmithKlein (GSK) listed OHS goals, statistics, and information including:

- 1278 recorded incidents—947 injuries (992 in 2006) and 331 illnesses (380 in 2006);
- injuries with and without lost time are due mainly to slips, trips or falls (safety and ergonomic hazards), over-exertions or strains and motor vehicle accidents;[6]
- lost-time illness stems mainly from mental ill health and musculoskeletal disorders; and
- musculoskeletal disorders are the main cause of reportable illness that does not lead to days off work (GSK, 2008a).

The company talks about the need for process safety (e.g., preventing major explosions), declaring that "Employee behaviour is the key to a safe workplace". After the March 2006 explosion at its U.K. Irvine site, a safety committee developed the Irvine EHS behaviour standard: "This defines the simple but important steps employees can take to improve safety, for example the importance of reporting all safety incidents, however small, including near misses. It also covers the negative behaviours employees should avoid" (GSK, 2008a, p. 109). AstraZeneca also is proud of its behaviour-based safety activities at its Newark and Wilmington sites in the U.S., and the "Get HIP U.S." program that rewards employees for participating (AstraZeneca, 2008).

This behaviour-based safety approach has been criticised for ignoring hazards and blaming individuals, avoiding root cause analysis, understanding of context and effective prevention activities, especially for health hazards. It may explain partly why GSK's 2007 audit found that its plants did well on the obvious safety hazards and were "generally weakest" on chemical

[6] The overall workforce in the sector has more injuries attributed to motor vehicle incidents than any other single source, according to the major companies.

exposure, resilience and mental well-being (i.e., stress), process safety, risk assessment processes, and ergonomics (GSK, 2008a, p. 107). There is no separate data for Canadian plants in this world-wide report.

Although the Pfizer website is purportedly a global one, statistics on their web site appear to be based on U.S. data only. They report that in 2007, Pfizer plants in the U.S. and Puerto Rico had five "enforcement events" related to EHS regulations; these cost the company $6,075, much less than the 12 that resulted in fines of $291,310 in 2004 (although it's likely most were environmental rather than OHS). Their lost-time injury and illness rate of 1.4 per 100 employees per year is above "the pharmaceutical industry standard" of 1.09; the company attributes this partly to collecting data from more facilities and from contractors and acknowledges that it must do better, particularly in terms of motor vehicle incidents (Pfizer, 2008).

AstraZeneca reports that in 2008, the company's overall occupational illness rate increased by five percent over 2007. Job-related stress illness accounted for 67 percent of all reported cases, Musculoskeletal disorders (MSDs) accounted for 19 percent and 80 percent of occupational illnesses required time off work (AstraZeneca, 2009).

3.3 Chemical and mineral hazards and their effects

Inhalation and skin absorption are the key routes of entry for chemical hazards. Figure 1, below, shows the factors increasing the likelihood of exposure to hazardous chemicals in pharmaceutical activities. Effects of chemical exposures range from acute skin rashes and breathing difficulties to chronic diseases and illnesses, such as reproductive health problems, cancer, and diseases of the respiratory system, liver, etc.

Pharmaceutical R&D work is designed to find and work with "new" chemicals that may be effective as drugs. For first products in a class of drugs, usually little is known at the outset about the hazards and effects of the NCEs, APIs, or intermediates produced in the manufacturing process. Substances must be tested with other chemicals, in biological media, on animals, etc., using protocols set by regulatory agencies in consultation with the industry. (Box 1 below tells a Canadian story about working with these kinds of reagents.)

Most studies and reports about pharmaceutical work health and safety focus on chemicals and, in particular, on measuring inhalation exposures. Appendix 1 lists some of the many chemicals present in pharmaceutical R&D and production facilities. Solvents dominate the list. Many of them have acute and chronic effects, including carcinogenicity and adverse reproductive outcomes. Little, if anything, is known about the effects of being exposed to several chemicals at one time, or when combined with other hazards. One reported outcome is that noise and solvent exposures produce hearing loss and balance problems because of their synergistic effects (Hodgkinson & Prasher, 2006).

Figure 1 Factors influencing risk of exposure to pharmaceutical substances (NCEs and CIs)

Evaluation criteria	**Increasing risk of exposure** →			
Physical form	Cream, ointment coated tablet	Solution, suspension	Uncoated tablet, granular solid	Micronized powder
Quantity handled	Small (mcg)			Large (kg)
Process	Contained, low aerosol and contact potential			Open, dusty, significant human contact
Procedures	Well-controlled			Poorly defined
Facilities and engineering systems	Physical isolation barrier technology	Well-designed and maintained ventilation	Traditional controls	Open process
Analytical methods: Industrial hygiene Biologic monitoring	Validated methods to assess exposures		Incompletely characterized methods	No analytical methods

Reported outcomes from exposure to APIs (using names or phrases from the original reports) include:

- chloramphenicol: affects blood and bone marrow (Jeebhay, Mbuli, & Uebel, 1993);
- cortisone: suppressed adrenocortical hormones (Newton et. al., 1978, as cited in Newton, Browning, Nicholson & Mowat, 1982);
- glucocorticoids: fat deposits on the back of the neck, rotator cuff and face while losing it on the extremities, skeletal muscle wasting, weight gain, fatigue, hypertension, personality changes, oedema, hemoglobin and red cell count increases, loss of menstrual period (Woolrich, 1988);
- penicillin: immunological reactions, changes in intestinal microflora (Shmunes, et al., 1976 and Vilanskaja and Steinberg, 1970, as cited in Naumann & Sargent, 1997).

Box 1

What happened at Sepracor?

In October, 2008, Roland Daigle died after working with a chromatographic analytical reagent at the Sepracor pharmaceutical plant in Windsor, Nova Scotia. On his hospital bed, the 46-year-old chemist named trimethylsilyl diazomethane as the substance to which he attributed the effects that led to his death (CBC, 2008; Tutton, 2008).

Like many chemicals, it has other names. Its CAS number—the equivalent of a fingerprint to identify the substance—is 18107-18-1. The chemical is said to be less toxic than pure diazomethane, but an extensive internet search of specific chemical databases and general sources yielded no information about its effects.

The situation is complicated by the fact that the chemical does not come on its own. In what seems to be typical, companies provide it in two mixtures—one with diethyl ether and another with n-hexane (Sigma Aldrich). In both products, the chemical is about 1/3 of the total concentration.

While there is no information about the silane diazomethane chemical (like most chemical substances and other products on the market today), diethyl ether and n-hexane are known as serious acute and chronic hazards in their own right (see New Jersey's Department of Health right-to know website, http://web.doh.state.nj.us/rtkhsfs/rtkhsl.aspx). Still, we don't know what happens when people are exposed to diazomethane mixed with either chemical.

Although Daigle pointed out the culprit chemical before his tragic death, and even though another chemist—a young man named Jason Siddell—died in New Jersey in 2007 after working with the same chemical (personal conversation), authorities do not appear to have acted on this lead. (There was no report from the Nova Scotia Department of Labour at the time of writing.)

North American legal and health and safety systems put the burden of proof on those who fall ill or die from exposure to a hazard, rather than on the substance, its producer or the employer who chose to buy it. The European Union's REACH chemical law (see Section 4.3.6. for more information), based on the precautionary principle and producer responsibility, shows that alternate approaches are possible.

There is more to the picture. Saying that it is "virtually unknown" how APIs get into workers' bodies and what happens afterwards, Belgian OHS researchers studied exposures to fentanyl dust, a synthetic narcotic (Van Nimmen, Poels, & Veulemans, 2006, p. 666). It turned out that the most important route of entry for exposure was through the skin—not inhalation, as was commonly assumed. This has consequences for setting standards, since occupational exposure limits assume workers inhale chemicals. It also may mean that many efforts by pharmaceutical company OHS staff to develop guidelines and procedures based on air monitoring are inappropriate and inaccurate. (For more detail on the guidelines, see section 4.)

Anti-neoplastic drugs are the focus of much attention in health care settings. Alkylating agents (types of antineoplastics or cytotoxic drugs) have been linked to menstrual changes and painful periods (amenorrhea) (Clement, 1997). There are recommendations to prevent exposure and,

thereby, the effects, which range from cancer to genotoxic/mutagenic changes and adverse reproductive outcomes (e.g., National Institute for Occupational Safety and Health, 2004).

However, these recommendations don't extend to the factories where the drugs are made. Dutch researchers found evidence of a common cytostatic drug in the breathing zone and urine of four lab and manufacturing workers, a result of contamination in the workplace (Bos, Weissenberger, & Anzion, 1998). A few years later, other researchers visiting a Dutch pharmaceutical plant noted: "State-of-the-art of protective equipment was high and regular monitoring was performed on the 'high risk' workers to ensure occupational exposure does not occur" (Meijster, Fransman, Veldhof, & Kromhout, 2006, p. 661).[7] This statement reflects a common approach to OHS, wherein the fact that protective equipment is in place leads to an assumption that workers are not being exposed to hazards, an assumption that may or may not be correct.

Allergies are also relatively common in drug production and R&D jobs. For example, since allergic reaction to *Povata* seed (psyllium and ispaghula) was reported in 1941, numerous cases of allergic rhinitis, asthma, anaphylaxis, and asymptomatic eosinophilia (high number of white blood cells) have been reported. Sensitization occurs after inhaling seed powder, particularly from powdered laxatives (Bernedo, García, Gastaminza, Bartolomé, Algorta, & Muñoz, 2008). In 1997, Korean doctors reported a 23-year-old female worker with occupational asthma and rhinitis. She had worked three years earlier with powdered serratial peptidase and lysozyme chloride, enzymes used in anti-inflammatory drugs (Park & Nahm, 1997). Other respiratory sensitisers reported in the literature include: cimetidine (Coutts et. al., 1984, as cited in Naumann & Sargent, 1997), salbutamol (Fawcett, Pepys, & Erooga, 1976, as cited in Teichman, 1988) and penicillin and cephalosporin antibiotics and enzymes, lisinopril, α-methyldopa, salbutamol, and opiates (Heron & Pickering, 2003).

Skin diseases are an important emerging hazard. In many European countries, these are the second most prevalent occupational disease (after musculoskeletal disorders). Pharmaceutical industry workers are among those affected (European Agency for Safety and Health at Work, 2008b). These diseases are caused by exposure to chemical, biological, and physical hazards. Stress aggravates allergic contact eczemas (delayed hypersensitivity) and urticarias (immediate hypersensitivity) (EurOSHA, 2008b).

APIs reported to cause skin problems include:

- alprenolol: dermatitis (Ekenvall & Forsbeck, 1978, as cited in Naumann & Sargent, 1997);
- azithromycin (Zithromax), an antiobiotic: affected about 25 percent of 20 Croatian workers handling the powdered drug and its intermediates, leading researchers to warn of consequences outside the workplace: "every case of occupational drug hypersensitivity may be an additional non-occupational health risk related to regular use of the drug in therapy" (Milkovic-Kraus, Macan, & Kanceljak-Macan, 2007, p. 102);
- bacampicillin (Stejskal, Olin & Forsbeck, as cited in Naumann & Sargent, 1997);
- cardiovascular drugs alprenolol and quinidine (Sargent & Kirk, 1988);
- n-(3-Trifluoromethyl- 4-nitrophenyl) phthalimide: allergic contact dermatitis to an

[7] The Dutch authors may be dealing with the same plant, or the facility in the earlier study may have closed. The authors of the later study said there is only one plant in the country making antineoplastic drugs.

intermediate in producing flutamide—despite being covered with special equipment: gloves, overalls and compressed air breathing apparatus (Jungewelter & Aalto-Korte, 2008);
- penicillin: allergic contact dermatitis (Type IV); and systemic urticaria probably including contact urticaria (Moore & Nygren, 2004); potent sensitizer and skin irritant (Watrous, 1947); and
- quinidine: dermatitis (Hardie, Savin, White & Pumford, 1978, as cited in Naumann & Sargent, 1997).

Closer to home, in 2004, University of Ottawa dermatologists reported allergic reactions in two men from a pharmaceutical company blending department. The reasons? "We believe, in conjunction with the occupational health department at the company, that these employees might not have followed safety precautions when entering or exiting the blending rooms, **as well as** there having been an inadequate ventilation system" (emphasis added) (Mimesh & Pratt, 2004).

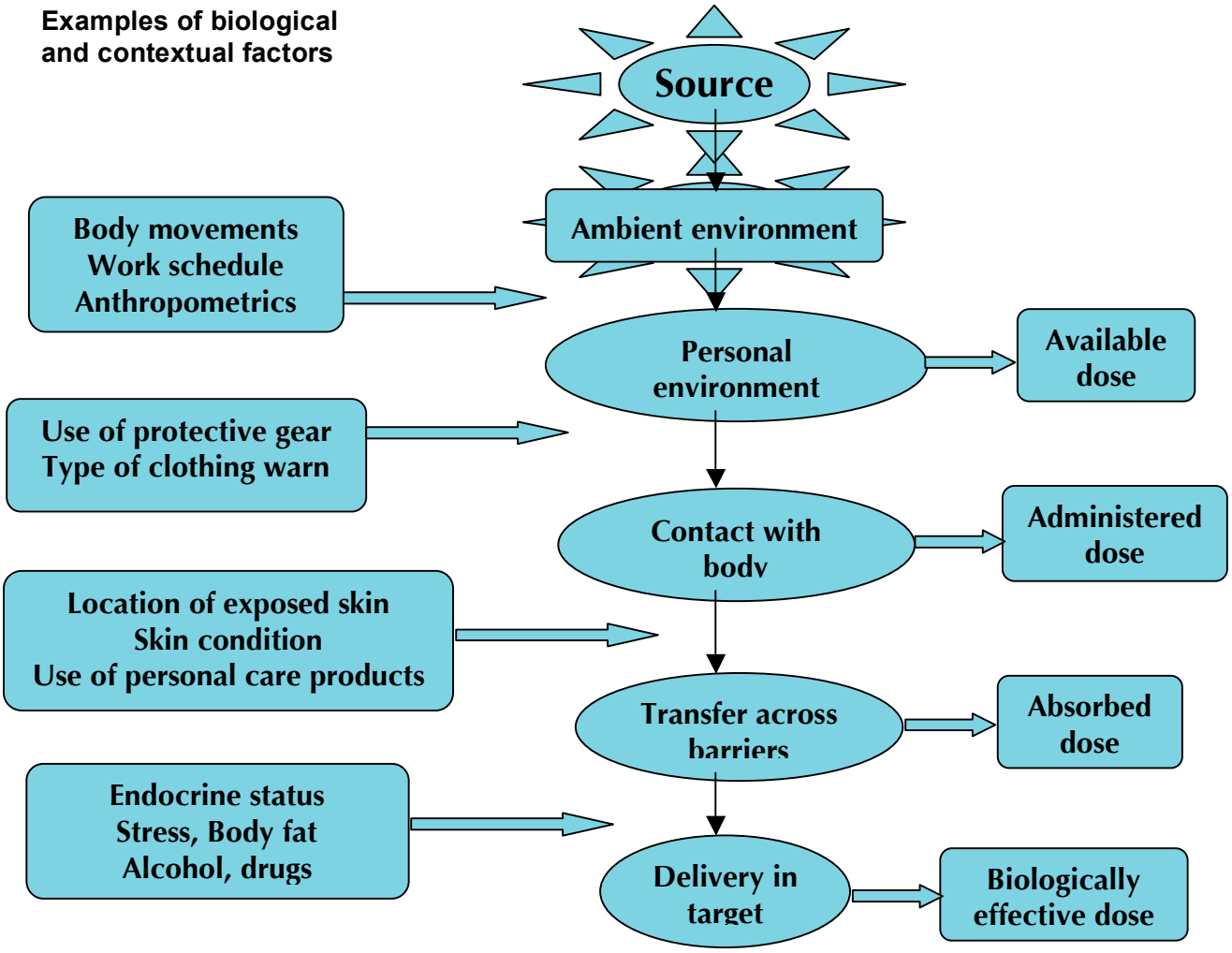
Nanotechnology also is a concern these days. Any type of exposure to these microscopic particles may have adverse health effects (Canadian Institute for Environmental Law and Policy; CTA, 2009); it most likely would occur during R&D, primary production and the early stages of secondary production processes. The National Institute for Occupational Health and Safety (NIOSH) has just issued an interim *Current Intelligence Bulletin* about hazard and medical surveillance for workers exposed to nanoparticles, partly due to a lack of information available about the associated hazards (NIOSH, 2009).

Whatever the chemical hazard, a Canadian researcher (Arbuckle, 2006) suggests that women's acute chemical exposures may have different consequences than those of men. She proposes three questions to address in looking at sex/gender differences:
- How do differences in personal environments affect contact with a chemical (assuming the same setting)?
- Does absorption differ across skin, lung, gastrointestinal wall and other barriers?
- Does the same amount of an active chemical or its metabolite reach target tissue?

Figure 2, below, shows the sample factors Arbuckle reviewed in coming to the conclusion that such differences may well exist. It is logical to expect that chronic effects may be different too. It also emphasizes the importance of careful attention to how chemical (and other hazard) exposures are studied. The authors of a review of studies looking at gender differences in occupational exposures echo Arbuckle's concerns. They cautiously concluded that "the validity of exposure estimates in epidemiology may be threatened by failure to consider possible gender differences along the pathway from sources to exposure measures" (Kennedy & Koehoorn, 2003, p. 582).

Figure 2

Examples of biological and contextual factors



Contextual and biological factors may differ for women and men in acute chemical exposures (Adapted from Arbuckle, 2006)

3.4 Biological and communicable hazards and their effects

This category of hazards includes viruses, moulds, bacteria, and blood-borne pathogens. Difficult to see, their effects can be both acute and chronic. They are quite common in R&D work, where you can find "virtually any human pathogen or organism" other biologists study, whether genetically engineered or unaltered (Klees & Joines, 1997). In one example, porcine pancreatic dust was connected to a 40 to 50 percent bronchial hypersensitisation rate among pharmaceutical workers during the 1980s (Weissmann & Baur, 1985, in Teichman et al., 1988).

Laboratory-acquired allergies to animals are fairly common, although communicable diseases spread by animals are less likely. Other reported hazards in this category include: brucellosis, encephalitis, *Escherichia coli,* hepatitis, herpes viruses, HIV, lab-acquired infections, leptospirosis, (mammalian and insect), Q fever, tissue culture cell lines, rabies, rat bite fever, shigellosis, *Streptomycetes,* tuberculosis, and vaccinia (Klees & Joines, 1997). Recently, there has been evidence of genetically modified organisms in some facilities (e.g., AstraZeneca, 2008).

3.5 Reproductive and genotoxic hazards and their effects

Reproductive hazards can affect female and male reproductive systems, sexual feelings, the ability and time to conceive healthy children, and the children themselves. More recently, the focus has been on endocrine disrupter chemicals (EDCs), including drugs, inside and outside the workplace (Hotchkiss et al., 2008; Lawson et al., 2006).

Despite the effects on and through men, historically, women's child-bearing potential has been the focus of employers, governments, policy-makers, and researchers in relation to this hazard (Canadian Advisory Council on the Status of Women, 1980; Miller-Chenier, 1982; Paul, Daniels, & Rosofsky, 1989; Stellman & Henifin, 1982). Women of child-bearing age were kept out of some jobs where exposures might lead to adverse reproductive outcomes. They seemed to have only two options: finding work in traditional female jobs (where reproductive hazards were not apparent) or sterilisation (Paul, Daniels & Rosofsky, 1989; Stellman & Henifin, 1982).

In 1976, General Motors (GM) Oshawa employee Jean Smith opted for sterilisation to keep her job working with lead-containing batteries. Other Canadian companies with exclusionary policies and practices included a Diamond Shamrock polyvinyl chloride plant (Reasons, Ross, & Paterson, 1981), the Atomic Energy Control Board, Hudson Bay Mining and Smelting, Inco, and Ontario Hydro (Levitsky, 1986). U.S. examples include six fertile women excluded from jobs with exposure to cancer therapy drugs at American Cyanamid labs in Pearl River, New York (Stellman & Henifin, 1982) and Johnson Controls. In the latter case, the Supreme Court ruled in 1991 that it was illegal to exclude women from lead areas while leaving men exposed to hazardous amounts of the metal (Graham, Lessin & Mirer, 1993). In the 1980s, Massachusetts employers in the chemical and electronics industries routinely used gender specific exclusionary and transfer practices "not justified by available scientific data" (Paul, Daniels, & Rosofsky, 1989).

A 1993 list of hazards linked to adverse reproductive health effects in workers (many of which are present in pharmaceutical work) includes ionising and non-ionising radiation, vibration, noise, temperature extremes, ergonomic hazards such as lifting and standing, hours of work/shift work and biological/ communicable hazards (e.g., from handling animals) (London Hazards Centre, 1993).

Hardin et al. (1981) examined the teratogenicity of 19 industrial chemicals, several of them used in drug manufacturing. Other American researchers built on a 1982 report by reviewing literature published between 1980 and 1985; pharmaceutical and general laboratory work, as well as hazards relevant to the industry appeared on their extensive list (Rosenberg et al., 1987).

Scandinavian research looked at spontaneous abortions among women in the pharmaceutical sector. They found this outcome increased by 3.5 times with exposure to four or more solvents, with methylene chloride thought to be one of the solvents responsible, and odds ratios of 4.2 for estrogen exposures (Taskinen, Lindbohm & Hemminki, 1986). They cited an earlier study that found pharmaceutical lab work increased the odds of spontaneous abortion, as did work in the industry generally (for members of the Union of Chemical Workers). The latter study also found a slight excess of malformations in children whose mothers worked in the industry (Hemminki, Lindbohm, Hemminki & Vaino, 1984, as cited in Taskinen, Lindbohm & Hemminki, 1986). Other APIs also have adverse reproductive effects, sometimes indirectly. Cyclophosphamide metabolites cause uterine and ovarian effects (Clement, 1997), while sulphonamide exposures for male pharmaceutical factory workers were linked to increased abortions and fewer live births in their wives (Prasad, 1996).

Ironically, early pharmaceutical industry reports of reproductive hazards related to men. The effects of exposure to diethylstilboestrol (DES – a synthetic estrogen) were first mentioned in the 1940s. A drug company physician said he knew of one instance in which DES manufacture was abandoned for fear of litigation because of its "feminizing effect" (Watrous, 1947, p. 122). In the late 1970s, NIOSH investigators found 25 instances of breast tenderness and enlargement—common side effects of estrogen exposure—in men working in the production area of a U.S. DES plant between 1969 and 1972. There was a "persistent history" of DES reactions year after year; high levels of DES in urine samples and adverse reactions turned up in medical tests. There was widespread DES contamination of buildings and equipment as far away as the lunchroom in a separate building (Shmunes & Burton, 1981). A 1977 Health Hazard Evaluation, done at the union's request, found DES "overexposure" in a Chicago pharmaceutical laboratory, not too far from the plant where Watrous worked (Meyer, 1978).

Other authors report diethylstilbesterol exposure linked to:

- hyperestrogenism: signs in five of 25 men and 12 of 30 women in Puerto Rico, and inter-menstrual bleeding in half the women, compared to one-sixth of controls (Harrington, Stein, Rivera, & De Morales, 1978);
- hyperestrogenism in workers and their children (e.g., Pacyński, Budzyńska, Przylecki, & Robaczyński, 1971);
- men found with nipple sensitivity, breast hyperplasia, enlarged breasts, decreased libido; women found to have irregular periods, headaches, nausea, breast pain, leucorrhea (cervical or vaginal discharge), ankle oedema (Zaebst, 1998); and
- menstrual disorders (increased flow and inter-menstrual spotting), gynecomastia (enlarged breasts in men), decreased libido (men) (Burton & Shmunes, 1973, as cited in Naumann & Sargent, 1997).

Closer to home, the Wyeth plant in Windsor, Ontario was the subject of scrutiny in the late 1970s and early 1980s. The union and its members were concerned, in particular, about ethinyl estradiol. It was classified by the International Agency on Cancer (IARC) as an animal carcinogen in 1974, and the company's own literature said it was a teratogen. The workers' starting point in their push for government and company action was reproductive hazards—a man with enlarged breasts and women with "menstrual complaints". Using a worker survey, Dr. John Marshall found evidence that male and female employees were exposed to the components of Ovral in sufficient quantities to lead to symptoms and serious adverse health effects commonly associated with oral contraceptive use (Nelson & Moure, 1980).

The survey was part of a campaign to get the company to reduce exposures to various contraceptive APIs and production substances, and to institute a medical surveillance program. Union investigations found other health effects (e.g., brain cancer, cardiovascular effects, hepatitis, and thyroid disorders). Workers used their right to refuse dangerous work and refused overtime. Government inspectors visited the plant several times, taking air measurements and checking ventilation systems; they did find problems (despite some atypical situations, according to Ministry of Labour documents) and recommended and/or ordered changes that were in line with some of the union's demands (Personal conversation, Windsor Occupational Health Information Service, 2009). The plant has since closed.

3.6 Carcinogens and their effects

Active pharmaceutical ingredients and common industry ingredients and intermediates seem to have earned more space in reports from the International Agency for Research on Cancer (IARC) than any other type of substance (IARC, 1981; IARC, 1987a; IARC 1987b; IARC, 1990; IARC, 1997; IARC, 2000). By 1990, they had looked at about 200 pharmaceutical agents or classes of chemicals; 23 were then considered human carcinogens and another 14 were in the 2A category of probable human carcinogens[8] (IARC, 1990). In late 2008, a group of 12 scientists reaffirmed that 20 pharmaceutical agents belong on the IARC's list of definite human carcinogens. Some, such as phenacetin and estrogen-only menopausal therapy, were moved up from other categories (Grosse et al., 2009).

A few studies have looked for cancer outcomes in pharmaceutical workers in North America and Europe. The findings include:

- in a U.S. plant study, excesses of respiratory cancer in male maintenance workers and in female production workers, increased relative frequencies of melanoma among males and of leukaemia among females in production (Thomas & Decoufle, 1979);
- increased cancer deaths among male British pharmaceutical workers, particularly urinary tract and pancreas, similar to results from a NIOSH 1984 study in Massachusetts and other studies (Baker, Russell, Roder & Esterman, 1986);
- increased risk of breast cancer among female Danish insulin production workers (and perhaps among long-term male workers), although causal links were not clear (Hansen, Olsen, & Larsen, 1994);[9]

[8] A complete list and PDF versions of monographs and supplements can be found at http://monographs.iarc.fr/ENG/Monographs/allmonos90.php

[9] Initially, the 165 women in the study had "significantly elevated odds" of breast, cervical and all sites cancers, and pneumonia. This changed when the analysis was re-done, partly because only two had "adequate work histories".

- "excess" urothelial tumours in men and women that could not be connected to specific substances, increased risk for acute leukaemia, a slight increase in breast cancers among women, two brain cancers where 1.6 were expected and small numbers but statistically significant results for cancer of the lip, peritoneum and pleura in the Pharmacia AB plant in Uppsala, Sweden (Edling, Friis, Mikoczy, Hagmar, & Lindfors, 1995); and
- possible connections between work with pharmaceutical agents and liver (primary hepatocellular) cancer in a multi-country European study, with references to positive findings linked in a 1993 French study to exposures to thorotrast, immunosuppressive drugs, anabolic steroids, stanozolol, clofibrate and azathioprine (Heinemann et al., 2000).

The International Labor Organisation (ILO) chemical safety card campaign produces worker-friendly information about chemicals and protection methods. Yet information about the connection between pharmaceutical exposures and cancer is underplayed in this important chemical hazard information database. In 2006, a U.S. researcher found only two (arsenic trioxide and cyclophosphamide) of the 13 Group 1 IARC carcinogens used in anti-cancer therapy in the database. "Viewing pharmaceuticals as chemical hazards is obviously a 'blind spot' for even the public health agencies charged with protecting worker safety (and health)" (McDiarmid, 2006, p. 603).

Meanwhile, the lack of attention to possible carcinogens took its toll in the former Wyeth plant in Windsor, Ontario in 1987. A 49-year-old man died of brain cancer. The provincial Workers' Compensation Board recognised the death as being work-related, but it refused to accept that formaldehyde exposure was the cause (Personal communication, Windsor Occupational Health Information Service, 2009).

3.7 Safety and mechanical hazards

In the U.S. last year, media attention relevant to pharmaceutical safety hazards focused on combustible dusts. The chairman and CEO of the U.S. Chemical Safety and Hazard Investigation Board (CSB) called on the Occupational Safety and Health Agency (OSHA) to adopt a comprehensive standard for these dusts. The Board made the recommendation after studying 281 combustible dust incidents between 1980 and 2005 in which 119 workers were killed and 718 others injured (CSB, 2008). In 2006, the CSB called a U.S. pharmaceutical packaging firm (West Pharmaceuticals) to task for a 2003 dust explosion that killed six employees, injured dozens of others, and destroyed the plant (CSB, 2006).

Pharmaceutical plants in the U.K. have also had explosions. In 2006, four GlaxoSmithKlein workers ended up in hospital after an explosion and fire occurred at the Irvine, Scotland plant. The company was fined £20,000 (BBC News, 2006). There had been an explosion and fire at the same plant in 1999. The third explosion in less than two months at the Corden PharmaChem facility in Cork, Ireland took the life of one worker in April, 2008. Another five workers were injured (Kelleher, 2008). There is as yet no accessible report about the cause(s).

3.8 Ergonomic design hazards and stressors

Ergonomics is about fitting jobs to workers' physical and psychological needs. While musculoskeletal disorders (MSDs) get most attention, ergonomics also deals with cognitive functions and understandings about the use of controls (e.g., on/off switches), colours (e.g., on computer monitors and other displays), and similar design features. Poor ergonomic design can

increase exposures to other hazards (e.g., awkward posture can affect exposure to a chemical, poor signals can lead to process safety situations).

Ergonomic hazards are behind the largest portion of accepted workers' compensation claims in Canada, and are high on the lists of reported injuries at pharmaceutical companies (GSK, 2008a; Pfizer, 2008). These hazards have been shown to be more common in women's work, where jobs tend to be more repetitive, monotonous, and stressful than in men's. Furthermore, the work is perceived and defined as "light," often making its ergonomic hazards invisible (Messing, 1998).

The U.K. Health and Safety Executive's website has a pharmaceutical industry ergonomics page in which it uses case studies to describe solutions for hazards such as hand scoops that forced poor hand and wrist postures, heavy tank lids, and poor pipette and syringe design (HSE, 2008). EurOSHA includes two pharmaceutical industry case studies in one of its ergonomics publications (EuroOSHA, 2008a; EuroOSHA, 2008c).

The largest pharmaceutical companies include ergonomics in their website sections about health and safety. GlaxoSmithKlein and Pfizer describe efforts by their ergonomic teams to solve specific problems, but these are the obvious "accidental" design flaws, not large-scale process changes that get to some of the complex ergonomic hazards that likely exist in the plant (Pfizer, 2008; GlaxoSmithKline, 2008).

Psychological stressors can lead to MSDs in the neck, shoulders and lower back; it can be hard to differentiate between the traditional posture, force and repetition hazards and the stressors linked to them (e.g., Leroux, Dionne, Bourbonnais, & Brisson, 2005). North American governments tend to ignore this category of hazards. Exceptions are the Quebec law about "psychological harassment," the use of which Lippel says has benefited women more often than men (Lippel, 2003), the Saskatchewan and Manitoba OHS regulations about harassment and/or violence at work, and recent amendments to the *Canada Occupational Health and Safety Regulations* to include violence as a stressor. In Europe, the story is very different. EurOSHA calls work-related stress "one of the biggest health and safety challenges in Europe" (EurOSHA, n.d., para 1). They have documented that related human distress and poor economic performance cost the EU-15 an estimated 20 billion Euros in 2002 and between 50 percent and 60 percent of all lost working days (EuroOSHA, n.d.).

Common effects of work-related stress include increased blood pressure and related cardiovascular disease, immune response changes, gastrointestinal diseases, depression, apathy, anxiety, and poor relations with others. One effect of particular interest to women is the relatively-recent connection made between working night shifts and breast cancer. IARC recently announced findings that long-term shift work, which disrupts circadian rhythm, appears to be carcinogenic (IARC, 2007).

Only one example was found of pharmaceutical workers being the subject of epidemiological work about job-related stressors and their effects. A Dutch study compared two sets of garbage collectors ("blue collar") with 267 pharmaceutical workers ("white collar"); about three-quarters of the three groups were men. Respondents were said to be typical of their worksites in terms of gender, age, occupational level, and departments. The stress levels reported were almost equal—

about 39 percent in all three groups. Pharmaceutical employees reporting stressors put them in this order of importance: work pressure (82.9 %), work organisation (67.2 %), relationships with supervisors and colleagues (65.7 %), physical working conditions (52.9 %), future prospects (42.9 %), payment (35.6 %), work content (29.9 %), and negative influence on private life (26.3 %). The Dutch report may be relevant in the Canadian context, given what we know about workplace stressors in production and R&D facilities here.

Other researchers and women's health advocates say that women's work is often more stressful than men's (e.g., when the double or triple day, family responsibilities, and unequal pay for work of equal value is taken into account). Fatigue is one adverse health effect cited (de Fatima Marinho deSouza, et. al., 2002).

3.9 Summary

Using epidemiological methods to investigate if an individual substance or exposure to a particular hazard "causes" cancer or other effects is well-accepted, but problematic. In pharmaceutical R&D and production processes, the small batch production campaigns make it difficult to find a large group of individuals exposed to one hazard continually. Exposure to intermediates and the focus on APIs/NCEs, rather than other substances, overall exposures, or hazard categories complicates the picture. In addition, epidemiological studies often:

- have recommendations for further study instead of action,
- rely on quantitative methods rather than qualitative ones that could answer the "why?" questions often discussed in the "limitations" section of a paper, and
- use levels of certainty (p values of .05) that are far beyond expectations of cause-effect relationships in any other field or practice (e.g., the law).

These problematic features are evident in a thorough review of the literature about OHS in this sector. Almost all published materials focus on individual chemicals, particularly NCEs and/or APIs, rather than on the real-life exposures to multiple chemicals that are often present along with the non-chemical hazards.

A gender analysis is essentially non-existent in reports about pharmaceutical OHS (except for some studies about women's reproductive health) and women are significantly under-represented among researchers in this field.

Finally, although the largest companies have published OHS goals and activities, the smaller facilities -- where most pharmaceutical sector employees work in Canada – do not typically have such comprehensive approaches. They also generally pay much less attention to anything but chemical and biological hazards that may be reduced by non-OHS regulatory requirements (e.g., good manufacturing practices, cleaning protocols, etc.).

4. Approaches to preventing and reducing exposure to hazards

4.1 Risk assessment and the precautionary principle

"Risk assessment" is the prevailing approach used to assess "acceptable" effects on health and the environment in both Canada and the U.S. The Canadian government describes risk assessment as "**scientific** evaluation that determines the **potential** harm or danger a chemical substance can cause to human health and/or the environment, and the ways in which humans or

the environment can be exposed to the substance" (emphasis added) (Environment Canada, 2007b, para 4). Pharmaceutical companies also refer frequently to "risks" and their assessment. GlaxoSmithKline's explanation of its corporate environment, health and safety policy is typical: "Environment, health and safety issues are managed through an integrated system that aims to ensure issues and **risks** are identified, standards are established, training is provided, targets set and audits conducted" (emphasis added) (GSK, 2008b, para 1).

But quantitative risk assessment is **not** the same as hazard assessment, as the latter involves looking for potential hazards in a workplace or other environment. Although risk assessment could follow a hazard assessment, the two have become confused, and notions of risk and hazard conflated. Canadian health and safety laws often refer to "risk," i.e., a potential problem, when "hazard"—the inherent problem—is more accurate.

Risk assessment requires establishing an acceptable level of harm. This is a key reason the approach is criticised by scientists, researchers and others, who see the question as "How much harm can we get away with?" (see, for example, Montague, 2006). Canadian OHS government agencies have not openly attached numbers to what is "acceptable". Some look to the U. S. Occupational Safety and Health Administration (OSHA), which considers "significant" an "occupational lifetime risk (over a 45-year period)" of one case of cancer or another material health effect in a group of 1,000 workers (Infante, 2001, p. 40). This approach is one reason there is no "war" on occupational cancer in the U.S., says a former regulatory official. OSHA's assumptions also differ from those of the U.S. EPA: "(S)hould we be comfortable with 30 minutes' exposure in the workplace being equivalent to a lifetime of community exposure?" (Finkel, 2008, p. 3).

Risk assessment approaches are also criticised for considering only quantifiable data, using hidden assumptions made by "experts" and going beyond the "scientific" to the political. Montague cites the example of the first EPA administrator, William Ruckelshaus, who said in 1984, "We should remember that risk assessment data can be like the captured spy: If you torture it long enough, it will tell you anything you want to know" (Montague, 2006, para 9).

U.S. and Canadian laws require "sufficient evidence of potential risk or toxicity of, or extensive potential exposure to, a chemical" before they can require manufacturers or importers to provide information. The dearth of such information leads to conundrums that have "meant testing and information development has not been required for the great majority of existing chemicals" (Denison, 2007, p. vii). The Canadian government is now trying to catch up with the situation, with its recent Chemicals Management Plan, designed to assess thousands of chemicals and decide whether and how to regulate their use (Environment Canada, 2007a).

Like many others, Tickner & Geiser (2004) argue that risk assessment is can confuse a lack of evidence with no evidence of harm, which leads to a bias against action in the face of uncertainty. For epidemiologist Kriebel, risk assessment is the "reactionary principle" that encourages the "one-chemical-at-a-time" regulation method that undermines progress rather than preventing cancer and other diseases (Kriebel, 2008, p. 3).

Alternatives exist, and are used elsewhere. The precautionary principle is a more appropriate public health approach to assessing hazards and making decisions about preventive action. The 1998 *Wingspread Statement on the Precautionary Principle* came from 31 outstanding scientists and activists (including three Canadians). Setting the context, they said that "existing environmental regulations and other decisions, **particularly those based on risk assessment**, have failed to adequately protect human health and the environment, as well as the larger system of which humans are but a part" (emphasis added) (Ashford, et. al., 1998, para 2). Furthermore,

> Where an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public bears the burden of proof. The process of applying the Precautionary Principle must be open, informed and democratic, and must include potentially affected parties. It must also involve an examination of the full range of alternatives, including no action (Ashford et al., 1998).

The European Environment Agency's *Late Lessons from Early Warnings* report has a range of examples of how risk assessment has failed, where the precautionary principle could have been used (Gee, MacGarvin, Stirling, Keys, Wynne, & Guedes Vaz, 2001).

4.2 Occupational exposure limits (OELs)

Occupational exposure limits (OELs) are a key component of the quantitative risk assessment/cost-benefit approach to occupational health. Official and unofficial standards for airborne chemicals, they usually are set by governments (sometimes after advice from a multi-stakeholder committee), industry associations, and/or an employer. OHS specialists and enforcement officials use them to judge acceptable levels of airborne chemicals and some other hazards.

Canadian health and safety laws usually adopt OELs known as Threshold Limit Values (TLVs). Set for many years by a private U.S.-based organisation, the American Conference of Governmental Industrial Hygienists (ACGIH), they are not intended as fine lines between "safe and dangerous exposures"; nor should they be used as legal standards (ACGIH, 1999). According to the ACGIH "nearly all workers may be repeatedly exposed day after day without adverse health effects" to these time-weighted averages for eight-hour days and a 40-hour work week; sometimes maximum or ceiling levels are set for 15-minute intervals (ACGIH, 1999).

TLVs have been criticised because of their limited coverage (looking at only one API at a time); their basis in assumptions and caveats that mean "nearly all workers" effectively excludes women and others who are not healthy white males; their failure to account for real life exposures to multiple substances and hazards; and inadequate or inaccurate allowances made for longer days and irregular work schedules. Some 20 years ago, several authors published serious criticisms about corporate influence on the setting of TLVs (Castleman & Zeim, 1988) and the correlation between actual workplace levels and TLVs, rather than health-protective OELs (Roach & Rappaport, 1990). The TLV Committee now has conflict of interest guidelines and has taken other measures to improve its reputation, but still works on a chemical-by-chemical basis and does not appear to apply the precautionary principle or other preventive approaches.

Other jurisdictions use very different criteria and have much more protective standards. For example, the European Union usually assumes exposed workers are healthy adults, although some countries also claim to protect sensitive subgroups. Normally, they do not apply to pregnant women and nursing mothers, and specific action is expected to protect these groups (EuroOSHA, n.d., para 4). A Scientific Committee on Occupational Exposure Limits (SCOEL) can determine standards for chemical agents, carcinogens and mutagens in the EU. (For details, see European Commission, n.d.).

NIOSH, OSHA and the ACGIH data include few APIs. This may explain why pharmaceutical companies and sector organisations have developed in-house exposure limits for APIs, using knowledge and experience from their facilities. Unfortunately, the same cannot be said for other chemicals used or produced in the process. Nevertheless, industry practices provide interesting lessons about the use of risk assessment and the problem with using OELs and air monitoring to determine if problems exist.

The Association of the British Pharmaceutical Industry (ABPI) produced its first version of guidelines for setting OELs in 1985. Agius criticised these guidelines on grounds similar to what Roach and Rappaport found in their analysis of TLVs. He noted that health effects can be missed by assuming a "working limit" -- whatever was present, rather than what might (not) be there -- is appropriate. A better method, he said, is a systematic approach, like that in the 1988 Control of Substances Hazardous to Health (COSHH) regulation Code of Practice, requiring employers to set OELs when they have enough information (Agius, 1989).

In 1988, ICI Pharmaceuticals OHS staff described developing their in-house "Provisional Hygiene Standards (PHS)" in response to the U.K. COSHH regulation. These provisional standards were "a judgement about a level at which risks of adverse effects is low enough to be discounted, ... [a line between] what we believe to be acceptable risk and less acceptable risk" (McHattie, Rackham & Teasdale, 1988, p. 105). They include eight assumptions that are said to have "reasonable consensual acceptance" among OHS professionals. But these company officials clearly chose a different path when it came to carcinogens. Without offering evidence, they responded to a 1985 U.S. government report that there is no threshold (i.e., "safe" level of exposure) for these deadly substances by saying: "We suggest that in the context of trying to assess the risk-benefit balance in deriving a PHS a more helpful statement is: '*For practical purposes* (italics in original), thresholds are considered to exist for all chemically induced adverse biological effects' (McHattie, Rackham & Teasdale, 1988, p.107).

The same year, Merck hygienists in the U.S. (Sargent & Kirk) reported their own process for developing workplace exposure control limits (ECLs) based on risk assessments from R&D data. While acknowledging that risk assessments are controversial, they nevertheless developed an equation, using many assumptions, to come up with a number. (The same formula is used, with variations, in other papers, e.g., Binks, 2003; Naumann & Sargent, 1997)[10] The equation is accompanied by many caveats, including:

[10] The formula is ECL ($mg/m^{)}$) = $\frac{\text{NOEL (mg/kg/day) * BW (kg) * } \alpha \text{ * SF}}{\text{V } (m^3/\text{day}) \text{ * S (days)}}$

NOEL is the "no observable effect level" based on a threshold for different effects (decided by those doing the studies). BW is the "average human body weight" (70 kg for men and 50 kg for women). V is the volume of air

- it is based on "average" body weight (women are left out of most of the other articles using this equation);
- it assumes that everyone breathes the same amount of air in eight hours, even though there are variations between and within groups of men and women, people working in hot/strenuous jobs and those sitting at desks, etc.;
- it assumes that all the substance is absorbed (which likely doesn't happen); and
- it assumes inhalation is the only route of entry (see Van Nimmen, Poels, & Veulemans, 2006 for evidence to the contrary) (Sargent & Kirk, 1988).

This shift to using R&D toxicological information led the industry to more performance-based measures. This takes advantage of data they already collect to meet government requirements related to the product's effect(s) on the end user, as well as many years of air monitoring results. (For details, see Binks, 2003).

In 1996, the Merck authors and four others described how ECLs had evolved (Naumann, Sargent, Starkman, Fraser, Becker, & Kirk, 1996). "Control banding" was developed as drugs became more potent and it was hard to accurately measure and analyse substances with very low ECLs. The originators recognised there are a limited number of possible prevention measures and many similar problems have been solved before. They were inspired by biosafety practices in labs handling highly pathogenic materials, the semi-conductor industry's clean room technology, and other extreme industrial and laboratory containment processes (NIOSH, 2008; Zalk & Nelson, 2008).

This generic method uses criteria and information about health effects and technologies and equipment to classify hazards and/or exposures from least to most serious categories; (see Figure 3 for the 1996 version of a performance-based ECL). Each "band" has specific prevention methods. Engineered processes and equipment prevent exposure. Prevention measures range from good manufacturing practices to encouraging robotics or remote operations (NIOSH, 2008, Naumann et al., 1996, Zalk & Nelson, 2008). Examples include ventilated enclosures, glove boxes, and using continuous liners or bags (Binks, 2003). Personal protective equipment provides "redundant protection". The need to have an OEL before taking action to prevent or reduce exposure is gone.

The use of control banding, or a variation of it, has spread. The U.K. COSHH Essentials uses control banding to adapt the *Control of Substances Hazardous to Health* regulation to help small and medium workplaces know when and how to deal with airborne toxic substances (HSE, n.d.). Using work by individual companies, the ABPI revised its guidelines for setting OELs and recommends a four-category simple exposure banding when individual OELs cannot be set (ABPI, 1995b). Because dusts are a major hazard in many pharmaceutical production processes, to complement control banding, some U.S. researchers are developing methods to evaluate how dusty pharmaceutical powders are, given the small amounts of an API or NCE available in R&D and early production phases (Boundy, Leith & Polton, 2006). NIOSH is starting to consider control banding as a basis for their recommendations (NIOSH, 2008). Others talk about using the approach for other hazards (e.g., nanoparticles) and in other countries (Zalk & Nelson, 2008).

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breathed in during an eight hour day (10 m^3). S is the time to reach a "plasma steady state". α is the percent of the compound absorbed. SF is a safety factor that traditionally is 100-fold. (Sargent & Kirk, 1988, p. 310)

Figure 3

Enrollment criteria	PB-ECL Category 1	2	3	4	5
Potency (mg/day)	> 100	>10 - 100	0.1 - 10	< 0.1	< 0.1
Severity of acute (life-threatening) effects	low	low/mod	moderate	mod/high	high
Acute warning symptoms	good	fair	fair/poor	poor	none
Onset of warning symptoms	immediate	immediate	may be delayed	delayed	none
Medically treatable	yes	yes	yes	yes	yes/no
Need for medical intervention	not required	not required	may be required	may be required immediately	required immediately
Acute toxicity	slightly toxic	moderately toxic	highly toxic	extremely toxic	super toxic
Sensitisation	not	mild	moderate	strong	extreme
Likelihood of chronic effects (e.g. cancer, repro., systemic)	unlikely	unlikely	possible	probable	known
Severity of chronic (life-threatening) effects	none	none	slight	moderate	severe
Cumulative effects	none	none	low	moderate	high
Reversibility	reversible	reversible	may not be reversible	may not be reversible	irreversible
Alteration of quality of life (disability)	no	no	yes/no	yes	yes

Adapted from Naumann, et al., 1996

The assumptions and criteria behind control banding seem to get OHS specialists beyond the need to measure (and therefore the need to develop OELs) before determining if a hazard exists and what to do about it; the concept also is transferable to other hazards and workplaces. However, the approach does not put substitution, the precautionary principle and related strategies on the front burner. It still is focused on controlling hazards, albeit more often with higher level and collective methods. As used in the U.K., control banding does offer possibilities for small and medium employers, like those in the Canadian pharmaceutical sector, to deal with hazards. However, there are other more tiered and participatory approaches to determine if a hazard exists and then take immediate preventive action. The SOBANE (Screening, OBservation, ANalysis and Expertise) method developed in Belgium and used elsewhere in Europe is one possibility that can more easily incorporate primary prevention measures such as substitution.[11]

[11] For more information on SOBANE, see www.sobane.be and Rankin, Todd & Wigmore, 2008.

4.3 Health and safety laws

4.3.1 Canada - general

The health and safety of workers in pharmaceutical R&D and manufacturing facilities is a provincial matter. Although they vary by jurisdiction, Canadian OHS laws share these features:

- the employer has a general duty to provide a healthy and safe workplace;
- the employer must fix hazards;
- employer duties lead to workers' rights to:
  - know about the hazards they may face,
  - refuse work that is dangerous/unsafe/unhealthy,
  - participate in identifying hazards and recommending solutions, usually through mandated joint health and safety committees or representatives (except in Alberta), and
  - no harassment for OHS activities (in a growing number of jurisdictions);
- governments are not required to enforce OHS laws (except in Prince Edward Island);
- emphasis is on the "internal responsibility system" -- expecting or requiring that the "workplace parties" deal with OHS issues before government enforcers get involved;
- a hierarchy of controls is the preferred method of addressing hazards, in which prevention is a token concept, while the precautionary principle, substitution and other environmental/public health principles are rarely invoked;
- threshold limit values are adopted as legal standards in most jurisdictions;
- most regulations deal with safety hazards and traditionally hazardous sectors where men dominate the workforce, such as construction and mining;
- recent changes in OHS laws and regulations have covered hazards that are common in women's work -- specific stressors (e.g., harassment, violence, working alone/in isolation) and ergonomic hazards (although employers in most jurisdictions have resisted vigorously);
- there is a trend to require comprehensive OHS programs, developed with joint committees and evaluated at regular intervals; and
- the employer's responsibility to deal with the stressors per se is rarely recognised or addressed in the law or during inspections and only Quebec provides compensation for some chronic stressors.

To avoid jurisdictional differences, governments adopted a common approach to the right-to-know about chemical and biological hazards at work in 1988. The Workplace Hazardous Materials Information System (WHMIS) is similar to the U.S. *Hazard Communication* standard and European laws, although the latter tend to be more comprehensive and use precautionary and substitution principles (e.g., the European Union's REACH law – see section 4.3.6 for more information).

The *Hazardous Products Act* and *Controlled Products Regulations*, co-ordinated through Health Canada, includes national standards (including toxicity criteria) . The federal and each provincial government adopted basically the same WHMIS regulation. The result is that no Canadian employer may allow "controlled products" to be used unless they have a material safety data sheet (MSDS), proper labels and workers trained in how to use the product and interpret the labels and MSDSs. Specific ingredients must be listed based on rules about concentration and properties such as toxicity, flammability, the ability to explode, etc. (Health Canada, 2008d).

Toxicity includes long-term effects; MSDSs must name carcinogens, mutagens, reproductive toxins and sensitizers from prescribed international lists (Health Canada, 2002a; 2002b). There are special procedures for "trade secrets" (Health Canada, 2008c). Biological hazards are covered by Division 3 of [WHMIS] Class D – Poisonous and Infectious Material" (Health Canada, 2008b).

Despite good intentions, the key information tools -- MSDSs -- are not doing their job. In 2007-08, the Hazardous Materials Information Review Commission found 2,288 violations in 284 trade secret product claims, an average of 8.06 each. Missing or inaccurate toxicological property information is by far the most common violation (Hazardous Materials Information Review Commission, 2008). MSDSs have been criticised for years for being inaccurate about health effects (particularly long-term ones), incomplete (in terms of required information), difficult/impossible to read or understand due to the technical language and layout, and the object of poor training and/or enforcement. These problems add up to low use and awareness of MSDSs in various workplaces (Nicol, Hurrell, Wahyuni, McDowall, & Chu, 2008). Although some pharmaceutical industry employees may understand these documents because of their technical training, there is no evidence that they pay more attention to MSDSs than other workers or understand their limitations.

4.3.2 Laws and regulations relevant to pharmaceutical R&D and manufacturing

There are no specific OHS laws for Canadian pharmaceutical facilities. However, some laws and regulations do apply to drug manufacturing and/or R&D facilities. Two WHMIS exemptions are relevant.

First, "drugs" (i.e., APIs) are excluded from the system (as are pesticides, cosmetics and consumer products) [12]. The pharmaceutical industry "indicated that the majority of such raw materials are currently in compliance with WHMIS" (Health Canada, 2007). The multi-stakeholder Food and Drugs Act Sectoral Committee agreed to let drug companies voluntarily comply with WHMIS for their raw materials (Health Canada, 2007, para 4).

This is expected to change in 2009. Health Canada is co-ordinating the Canadian position for the Globally Harmonized System for the Classification and Labelling of Chemicals (GHS). The goal is effectively a more universal right-to-know about workplace chemical hazards. A consensus document, the GHS is a "standardized protocol for the toxicological basis for assigning chemicals to standardized hazard statements on labels and safety data sheets" building on the European Union's "risk phrase" (R-phrase) process (Zalk & Nelson, 2008, p. 338). Under this system, drugs will have to have MSDSs and all MSDSs will require more information than is currently the case under WHMIS. The GHS, which took effect in the European Union in January 2009, was to have been implemented in Canada in 2008 (Canadian Centre for Occupational Health and Safety, 2008).

The second exception is that laboratories don't have to follow all the labelling and MSDS rules if chemicals are used only in the lab for R&D (Health Canada, 2007a). However, section 30 of

[12] WHMIS rules followed those of the US *Hazard Communication* standard with exemptions for drugs, pesticides, consumer products, etc. The new European REACH regulation includes them.

British Columbia's *Occupational Health and Safety Regulation* does have specific requirements for laboratories. It and other parts of the regulation (e.g., section 6.34(1)(d)(iii) about "exposure control plans" for biological agents in labs) require employers to deal with hazards in accordance with the latest editions of WHO's *Laboratory Biosafety Manual* and Health Canada's *Laboratory Biosafety Guidelines*. Records of exposure to biological hazards must be kept (http://www2.worksafebc.com/publications/OHSRegulation/Part30.asp).

4.3.3 Laws and regulations requiring use of the precautionary principle, substitution, toxics use reduction and other primary prevention methods

The precautionary principle often is cited as the best approach to prevent exposure to carcinogens. A 2006 survey about how Canadian health and safety laws deal with carcinogens identified only 24 specific human carcinogens and these are regulated inconsistently by different jurisdictions. British Columbia, Alberta, Manitoba, Ontario, Quebec and Saskatchewan had established designated lists of substances with special attention to the handling, use, and OELs for carcinogens (Hosein & Deffie, 2006, as cited in National Committee for Environmental and Occupational Exposures, 2006).

British Columbia's *Occupational Health and Safety Regulation* requires use of the precautionary principle in section 6.34 about "exposure control plans" for some biological substances. The principle is defined as "adopting provisional precautions covering all routes of transmission, based on a higher level of protection, when the identity, aetiology or routes of transmission of the biological agent is designated as a hazardous substance" (http://www2.worksafebc.com/publications/OHSRegulation/Part6.asp#SectionNumber:6.34).

If workers are exposed to one of these hazards, the employer must develop and implement a plan based on the principle. Among other things, the plan must include:

- a risk assessment to determine if workers may be exposed to the substance;
- engineering and administrative measures to eliminate or minimize the possibility of exposure;
- infection control precautions and transmission-based precautions; and
- a program to inform workers about the plan and to provide education, training and supervision so they can work safely with or near the hazard.

Section 5.54 sets out the rules about when plans are required. If so, section 5.55 requires the employer to start by considering substitution along with engineering or administrative controls. (http://www2.worksafebc.com/publications/OHSRegulation/Part5.asp#SectionNumber:5.55)

British Columbia also follows a European Union ban on three specific carcinogens (4-aminodiphenyl, 3,3-dichlorobenzidine, 4-nitrodiphenyl) and has special rules for "designated substances", including carcinogens from the ACGIH A1 and A2 and IARC 1, 2A and 2B lists, reproductive toxins (as defined by ACGIH), sensitizers (also classified as such by the ACGIH), and chemicals with an ACGIH "L endnote" (exposure by all routes should be carefully controlled to levels as low as possible). Section 5.57 of the regulation (http://www2.worksafebc.com/publications/OHSRegulation/Part5.asp#SectionNumber:5.57) says these substances must be replaced with less hazardous ones, if practicable. If replacement is impossible, the employer must develop and implement another exposure control plan to keep workers' exposures as low as reasonably achievable below the OEL (essentially the TLV). Guidelines explain that exceptions are made for those "currently not considered feasible for B.C.

workplaces. This exception is limited to formaldehyde, styrene, and wood dust (all forms)" (G5.48-1 Table of exposure limits - background information. Retrieved from www2.worksafebc.com/Publications/OHSRegulation/GuidelinePart5.asp.)

Building on the designated substance provision, there is a "protective policy" for reproductive toxics and sensitizers. For the latter, protective reassignment is also an option and the policy and procedures must identify ways to get rid of or minimize exposure for workers who are or may be sensitized to a substance (Section 5.58 www2.worksafebc.com/publications/OHSRegulation/Part5.asp#SectionNumber:5.58).

Part II of the *Canada Labour Code's* requirements about preventive programs is clearer than the B.C. regulation about the priorities for prevention. Once hazards are identified and assessed, employers shall "take preventive measures to address the assessed hazard in the following order of priority": a) eliminate the hazard; b) reduce the hazard, including isolating it; c) provide personal protective equipment, clothing, devices or materials; and d) administrative procedures. Preventive measures must not create a hazard and must take into account the effects on the workplace [Section 122.2].

Substitution also is named in the federal health and safety law. Part X (Hazardous substances) of the *Occupational Health and Safety Regulations* in the *Canada Labour Code* says no one may use a hazardous substance "where it is reasonably practicable to substitute a substance for it that is not a hazardous substance". [Section 10.16. (1)] Furthermore, if a less hazardous substance that serves the same purpose is available, it "shall be substituted for the hazardous substance where reasonably practicable". [Section 10.16. (2)] (http://laws.justice.gc.ca/en/showdoc/cr/SOR-86-304/bo-ga:l_X//en?noCookie)

Division 5 of Quebec's *Regulation Respecting Occupational Health and Safety* also calls for replacement (i.e., substitution) of hazardous substances in workplace air: *"*Insofar as possible, dangerous substances that are sources of dusts, fumes, mists, vapours or gases shall be replaced with substances that are not dangerous or are the least dangerous possible" (Section 39). (www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=%2F%2FS_2_1%2FS2_1R19_01_A.htm)

Manitoba uses the term "designated materials" (carcinogen, mutagen, respiratory sensitizer, reproductive toxin, foetotoxin or teratogen under the *Controlled Products Regulations*). If air measurements detect a designated material, the employer must establish an OEL as close to zero as possible; it cannot be more than the TLV, where one exists [*Workplace Safety and Health Regulation*, Section 36(5)(1)(b)]. (http://safemanitoba.com/uploads/regulations/part36.pdf)

Despite the attention to carcinogens and other especially-toxic substances, almost all of these laws are rooted in traditional occupational hygiene approaches: identify, assess, evaluate, control. This means nothing is done until air measurements are made. In some cases, OELs must also be considered, meaning that exposures will be controlled rather than eliminated.

4.3.4 Laws and regulations or particular relevance for women

Only four jurisdictions make special mention of OHS issues relevant to women. The best known and most comprehensive is Quebec's "retrait préventif", introduced in 1981 (sections 40 - 48 of

the *Act*). A Quebecoise pregnant or nursing worker exposed to hazards that may affect her health or that of the foetus or her child has a legal process to follow to avoid those hazards. If the employer does not allow the preventive action, she may stay away from work until appropriate work is provided, the child is born or she stops breastfeeding. Off the job, she receives 90 percent of her net salary from a compensation board fund to which all employers contribute, regardless of how many female workers they employ. There are rules against reprisals. Women must get their old jobs back without penalties in terms of wages or benefits.

Almost 20 years later, the federal OHS law -- Part II of the *Canada Labour Code* -- was changed to give pregnant and nursing women additional rights. Section 132(1) says a pregnant or nursing worker may stop doing her job if she believes that continuing her job while pregnant or nursing may be hazardous to her health or to that of the foetus or child. She must then talk to her doctor as soon as possible, to determine if anything she does at work could harm her health or that of the foetus or child. She may be reassigned while waiting for the decision. Whether or not she is reassigned, she must be paid her regular wages and benefits while the doctor makes a decision. Division VII in Part III of the *Code* covers the reassignment process. Employers presented with a reassignment or job change request and a medical certificate must comply if it is "reasonably practicable". The onus is on them to show otherwise. If no job is available, the employee can take a leave of absence for up to the 24th week after the birth (http://laws.justice.gc.ca/en/showdoc/cs/L-2/bo-ga:l_III-gb:l_VII//en#anchorbo-ga:l_III-gb:l_VII).

Manitoba added a small section about pregnant or nursing workers in the 2006 consolidated *Workplace Safety and Health Regulation*. Under general duties, section 2.5 puts the onus on a woman to tell her employer that she is pregnant or nursing. Once this is done, the employer must let her know about "any known or foreseeable risk that conditions at the workplace pose or may pose to the safety or health of the worker or to her unborn or nursing child"; and to the extent that is "reasonably practicable"[13] minimize her exposure to the hazard or, if available, provide alternate work that does not present hazards to the woman or her foetus/child, without loss of pay or benefits.

The B.C. regulations about "designated substances" are useful tools for female workers. If a substance listed by the ACGIH as a reproductive toxin[14] is present in the workplace, section 5.57 requires the employer to replace it with a less hazardous material, "if practicable". If this is not the case, the employer must implement an "exposure control plan" using the "as low as reasonably achievable" (ALARA) principle[15] and at least less than the substance's OEL (usually a TLV). The regulation goes further, requiring the employer to develop appropriate policies and procedures that "may include protective reassignment". Workers must be told about the

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[13] "Reasonably practicable" has a legal meaning from the U.K. case *Edwards vs. The National Coal Board*. Essentially, the cost of doing nothing or little must be weighed against the cost of properly dealing with a hazard. "Costs" must be considered for money, time and effort. There must be a "gross disproportion" between the costs of fixing/preventing the hazard and doing nothing or little. Only then can the employer successfully argue they do not have to deal with the hazard.

[14] WHMIS uses the U.S. National Toxicology Program (NTP) -- http://cerhr.niehs.nih.gov/ -- and reproductive toxins on the list created by California's Proposition 65 -- http://www.oehha.ca.gov/prop65.html.

[15] ALARA comes from the nuclear industry, where radiation exposure is supposed to be reduced using this principle.

reproductive toxin. The policy and procedures must include ways to minimise exposure to a reproductive toxin if workers tell their employer about their intent to conceive a child or that they are pregnant. The requirements do not exclude men (Section 5.58).

4.3.5 United States

The U.S. *Occupational Safety and Health Act*, passed in 1970, does not cover all workers (especially in the public sector and "right-to-work" states). Twenty-six states have their own OSHA-approved plans. The Act's standards (essentially regulations) are mostly about safety hazards. Those relevant to pharmaceutical R&D and production workers include:

- Recording and reporting occupational injuries and illness (Part 1904)
- Process safety management of highly hazardous chemicals (1910.119)
- Toxic and hazardous substances (including specifics about 13 carcinogens including formaldehyde and methylene chloride) (1910 Subpart Z)
- Hazard communication (1910.1200)
- Occupational exposure to hazardous chemicals in laboratories (1910.1450)
- Blood-borne pathogens (1920.1030. (www.osha.gov/pls/oshaweb/owasrch.search_form?p_doc_type=STANDARDS&p_toc_level=0&p_keyvalue=&p_status=CURRENT)

Individual chemicals and other hazards are regulated on a case-by-case basis that typically takes years of extensive hearings and sometimes litigation. The lead regulation (1910.1025) includes an innovative medical removal protection program for men and women planning to have children. Workers who are reassigned for this reason must have their wages, benefits and seniority protected for up to 18 months.

Three states -- Massachusetts, New Jersey and Oregon -- have regulations about toxics use reduction. This pollution prevention strategy aims to have fewer toxic substances used and produced in the environment and workplace, and smaller volumes if substitutes are not available.

The Massachusetts Toxics Use Reduction Act (TURA) is the most extensive, effective, and well-funded (Toxics Use Reduction Institute, 2008). This 1989 law requires companies to prepare toxics use reduction plans in which they assess how and why toxic chemicals are used at their facility, and evaluate options for reductions. Implementation, however, is not required. Like a lot of these types of laws, TURA uses a cut-off amount (over 10,000 pounds) for listed chemicals; many are carcinogens and reproductive toxins. Toxics use reduction is defined in this law as changes made "**without shifting** risks between workers, consumers or parts of the environment" (emphasis added) (TURA, as cited in Roelofs, Moure-Eraso, & Ellenbecker, 2000, p. 843).

While the Act and its related Toxics Use Reduction Institute have been successful in many ways, occupational health and safety effects may be inadvertent and/or not considered in the rush to obey environmental laws, save money, and rationalise production processes (Roelofs, Moure-Eraso, & Ellenbecker, 2000). A 2002 paper about moving from toxics reduction to the precautionary principle demonstrates the point (Mayer, Brown, & Linder, 2002).

4.3.6 European Union

The European Union (EU) has taken a somewhat different approach than the U. S. and Canada for some of its health and safety laws. The Registration, Evaluation, Authorisation and

Restriction of Chemical substances regulation (REACH) took effect in June, 2007. Although the final form of REACH is watered down relative to the original version, it remains innovative. REACH links improvement of occupational and environmental health "through the better and earlier identification of the intrinsic properties of chemical substances" (European Union, 2009). Key components and goals of REACH are:

- shifting the burden of proof about chemical health and safety from regulators to manufacturers and importers, requiring them to provide information about their chemicals;
- protecting human health and the environment from existing and "new" chemicals;
- using a phased-in approach, requiring registration of about 30,000 chemicals produced or imported in quantities of one metric ton or more per year per producer or importer;
- requiring chemical safety reports when registering about 20,000 substances produced in quantities of up to 10 tonnes a year, and special government authorization for the use of some 2,500 of the most hazardous chemicals;
- guided by the precautionary principle, encouraging substitution of the most hazardous chemicals by healthier and safer technologies and substances (substitution is not required if companies can show that the chemical's hazards are controlled or there are no suitable alternatives and the benefit outweighs the risk);
- establishing a new European Chemicals Agency to manage system databases (including one for the public) and co-ordinate in-depth evaluation of suspicious chemicals; and
- supporting innovative approaches in the EU chemical industry (European Union, 2009; Gap analysis).

In addition to REACH, the European Union has a tiered set of health and safety laws and regulations called directives. Additional directives are set by the 1989 Framework Directive (*Council Directive 89/391/EEC on the introduction of measures to encourage improvements in the safety and health of workers at work*). Provisions include "prevention principles" such as avoiding hazards and:

- "adapting the work to the individual, especially as regards the design of work places, the choice of work equipment and the choice of working and production methods, with a view, in particular, to alleviating monotonous work and work at a predetermined work-rate and to reducing their effect on health;
- replacing the dangerous by the non-dangerous or the less dangerous;
- developing a coherent overall prevention policy that covers technology, organisation of work, working conditions, social relationships and the influence of factors related to the working environment; and
- giving collective protective measures priority over individual protective measures" (European Union, 1989).

Some EU laws specifically relevant to pharmaceutical workers include:

- protection from biological agents at work (Directive 2000/54/EC) (European Union, 2000);
- protection from chemical agents (Directive 98/24/EC) (European Union, 1998); and
- protection from occupational carcinogens (Directive 90/394/EEC) (European Union, 1990).

These laws tend to be more prevention-oriented than North American ones. For example, the chemical agents directive says that when hazardous chemicals are present (air measurements aren't a required part of the process), the employer shall ensure the risk is eliminated or reduced to a minimum. Substitution is the preferred method (European Union, 1998). The carcinogens directive says employers must reduce their use "in particular by replacing it, in so far as is technically possible" with substances or processes that are not hazardous or are less so. The precautionary principle is mentioned directly (European Union, 1990).

Directive 92/85/EEC covers pregnant and breast-feeding workers. Among other things, it says they cannot be forced to do tasks for which the required assessment showed that they might be exposed to specific hazards and working conditions (many of which are found in pharmaceutical work) and they are not obliged to work at night during their pregnancy and for a period following childbirth, subject to providing a medical certificate (European Union, 1992).

Scandinavian countries historically have been far ahead of most others on the health and safety front. Occupational exposure limits in Sweden were held out for years as being more protective than TLVs; when an Ontario committee started investigating other OELs in the 1990s, they found that Norwegian solvent OELS were half those of Sweden's. Since the 1980s, Denmark, Norway, Sweden and Finland (the Nordic countries) have required companies putting chemicals into their markets to register with the Nordic Product Register. This affects the general environment, but also has positive implications for workers. The Register overlaps with some REACH rules, but requires more information about more things and will add value when REACH is in effect (Ahrens & Reihlen, 2007).

The SPIN (Substances in Preparations in the Nordic Countries) database provides the public with non-confidential, summarised information about the use of chemicals in different types of products and industrial areas listed in the Nordic Product Register. Financed by the Nordic Council of Ministers, Chemical group, it includes 22,000 substances. More than half are not in the EU information system on existing substances (ESIS), mostly because SPIN covers substances below 10 tonnes/year. SPIN also has information about polymers, substances not registered elsewhere in Europe and exempted from REACH (Ahrens & Reihlen, 2007; Nordic Council of Ministers, 2009).

4.3.7 Environmental laws

Although toxic chemicals are usually produced in a workplace, the primary law governing their management in Canada is environmental. The federal *Canadian Environmental Protection Act* (CEPA), last revised in 1999, is jointly administered by Environment Canada and Health Canada. From an occupational health perspective, useful features are:

- its goal of protecting human health and the environment;
- the framing statements about principles of sustainability, pollution prevention, the precautionary principle, polluter pays, the weight-of-evidence approach to decision-making, and using a life cycle approach;
- the Domestic Substances List (DSL), a compilation of about 23,000 substances used, imported or manufactured in Canada for commercial purposes between January 1, 1984, and December 31, 1986, in quantities of more than 100 kg per year;

- requiring that those substances be categorised to determine which need more detailed assessments and consideration as toxic substances—the Chemical Management Plan (CMP);
- a tiered notification system that includes a New Substances Notification process (that can contribute names to the DSL) and a Non-Domestic Substances List of chemicals accepted as being in commercial use elsewhere, which aren't on the DSL;
- requirements to report releases of some "pollutants" (less than 400), summarised in the National Pollutant Release Inventory (NPRI) and made available on the internet; and
- "toxic substances" require government action (e.g., regulation, pollution prevention plans, voluntary guidelines or memoranda of understanding) (Cancer and the Environment Stakeholder Group, 2007, Denison, 2007; Environment Canada, 2007a; NCEOE, 2006).

Under the CMP, more extensive screening and other follow-up is being carried out for about 4,300 substances. Five hundred of these are "high priority" for action.[16] While there are criticisms about this substance-by-substance approach, and questions about how assessments can be made without data, the process has generated interest in toxic substances, at least in terms of the environment and community in general (Canadian Environmental Network, 2009).

Another environment-related strategy has workplace consequences. An Ontario coalition (Canadian Environmental Law Association, 2008b) has been promoting—somewhat successfully so far—a provincial toxics use reduction law that would provide for improved workplace health and safety, among other things. The coalition's model bill defines toxics use reduction in a similar manner to the Massachusetts TURA and says it:

> ".. shall be achieved through input substitution, product reformulation, production process redesign or modification, production process modernization, improved operation and maintenance of production process equipment and methods, or recycling, reuse, or extended use of toxic substances by using equipment or methods that become an integral part of the production process of concern, but does not include incineration, transfer from one medium of release to other media, off-site or out-of-production process waste recycling, or methods of end-of-pipe treatment of toxic substances as waste" (CELA, 2008a).

In the U. S., the *Toxics Substances Control Act* and the *Emergency Planning and Community Right-to-know Act 1986* (EPCRA) are two key laws that fall under the Environmental Protection Agency (EPA) but have OHS consequences. The Toxics Release Inventory (TRI) was developed as a result of EPCRA and expanded under the 1990 *Pollution Prevention Act*, another EPA law. It makes public information similar to the Canadian NPRI, with more details and greater coverage. A number of groups have developed user-friendly mapping tools to use the data and integrate it with other information that is useful for both occupational and environmental health purposes (e.g., RTKnet.org and www.mapcruzin.com).

California is currently the main site of action on toxic substances in the U.S. While their emphasis is on environmental issues, their initiatives have occupational components or effects

[16] For details about criteria, processes, etc., see Denison's report for Environmental Defence and Pollution Probe, *Not That Innocent* and the Environment Canada Chemicals Management Plan website.

relevant to pharmaceutical R&D and production. The 1986 *Safe Drinking Water and Toxic Enforcement Act*, also known as Proposition 65, requires labelling of products containing carcinogens or reproductive toxins (the list is about 18 pages as of December, 2008). As businesses do not want to be associated with causing cancer or reproductive effects, the labelling requirement has resulted in fewer toxic substances in the workplace. Other California state initiatives include:

- the first U.S. state-wide environmental contaminant biomonitoring program (SB 1379), which became law in September, 2006 (California Department of Public Health, 2007);
- the partner Chemical Detection bill (AB 289), effective January, 2007, that lets state agencies get analytical test methods from chemical manufacturers, rather than having to figure them out themselves (Environment California, 2006); and
- a green chemistry initiative, the final report of which:
  - led to two laws: AB 1879, requiring the Department of Toxic Substances Control to adopt regulations by 2011 that identify and prioritize chemicals of concern, evaluate alternatives, and develop regulatory responses for chemicals of concern in products, and SB 509, that creates a public Toxics Information Clearinghouse, and
  - has six recommendations that effectively integrate occupational and environmental health issues in an approach using expanded pollution prevention measures and other tools in moving towards a "cradle-to-cradle economy" (California Environmental Protection Agency, 2008).

5. Rules, guidelines and best practices in the pharmaceutical industry

5.1 Canadian best practices examples

Pollution prevention (P2) involves reducing or eliminating waste at the source. This concept is meant to be the cornerstone of CEPA, where it is defined as "The use of processes, practices, materials, products or energy that avoid or minimize the creation of pollutants and waste, and reduce overall risk to human health or the environment" (Environment Canada, n.d.). This is slightly different than the trend-setting EPA definition (EPA, 2009).

Like other environmental efforts, pollution prevention can also prevent and reduce workplace exposures to hazards. An example, cited in several reports, comes from a Canadian generic pharmaceutical company. Novopharm responded to NPRI reporting requirements using P2. The Scarborough, Ontario plant, with about 1000 employees, was the largest single Canadian emitter of the carcinogenic solvent dichloromethane (methylene chloride). In five years, the company changed from a solvent-based pill coating process to one that is water-based. Reported methylene chloride air emissions are much reduced now and workers' exposures have been eliminated. The company's average annual savings in chemical purchasing costs were $1 million a year (NCEOE, 2006).

5.2 Pharmaceutical company approaches and best practices

The large pharmaceutical companies generally combine environmental and OHS issues (EHS) under the rubric of "corporate responsibility" or a similar term. They have statistics, programs, goals, metrics, reports, newsletters, guidelines, and documents developed by and for their EHS staff. There tends to be much more emphasis on environmental issues than on OHS, and EHS topics are evident only on the global or corporate websites, not the national ones.

All companies with accessible materials have similar themes. The corporate AstraZeneca web site lists a core priority as "(p)roviding a safe workplace and promoting the health and wellbeing of all our people" (AstraZeneca, 2009). The corporate GSK web site refers to a goal to "eliminate all work-related injuries and illnesses" and states that "(s)upporting the health of employees helps increase energy levels, engagement and productivity" (GSK, 2008). At the time of writing, 23 of its 80 manufacturing sites, and one R&D site, are certified to the international health and safety standard OHSAS 18001. All manufacturing sites are supposed to be certified by the end of 2010; Canadian facilities are not yet certified. GSK documents describe activities such as:

- setting targets to reduce the number of musculoskeletal disorders by five percent each year to 2010;
- integrating ergonomic principles into the design of major projects and the purchasing of furniture and equipment;
- making 80 percent of operations that handle hazardous compounds 'respirator free' for routine production tasks by 2010;
- a "team resilience program" that started in 2003, available in 12 languages and used in 41 countries, in which employees and managers identify sources of pressure and agree how to address them and avoid "stress";
- the use of "green chemistry" in API development (GSK, 2008a; GSK, 2008b).

AstraZeneca and Pfizer have similar web pages and documents (e.g., Pfizer, 2009, para 1). Both companies emphasize personal responsibility, individually oriented health promotion and behaviour-based safety programs. At Pfizer, "safety" takes precedence in their specific goals and commitments to:

- improve safety performance;
- provide a workplace where chemical and physical hazards are appropriately managed;
- establish a culture where all colleagues prioritize safety and constantly demonstrate care and safe behaviour;
- ensure the medical well-being of our colleagues in the workplace;
- make certain our operations are not at risk of an accidental chemical release, fire, explosion or any other unexpected process upset;
- safeguard those in the workplace from adverse exposure to chemical hazards;
- protect the safety of our drivers and those who share the roads with them" (Pfizer, 2009, para 2).

An independent report describes changes in an unnamed U.S. pharmaceutical plant, where workers used to have to wear powered air-purifying respirators to prevent exposure to pharmaceutical powders. Results of changing the process to improve the capability of containment bags included:

- employees were not directly exposed to pharmaceutical powders;
- operator exposure rates were significantly reduced;
- reduced personal protective equipment (PPE) usage saved $172,800 a year;
- reducing employee time to put on PPE saved $78,000 each year;
- 40 percent reduction in non-hazardous waste generation and less waste requiring disposal;
- less IH sampling was needed to verify exposures ($30,000 per year); and

- positive risk management changes included assurance of regulatory compliance, potential Food and Drug Administration and European Medicines Agency (FDA/EMEA) benefits for contained processing, and less processing area to be cleaned (American Industrial Hygiene Association, 2008).

For transnational companies, "green chemistry" is an important aspect of most OHS/environmental health programs. This term, coined in the early 1990s, is based on 12 principles, many of them about reducing waste and dealing with toxic substances (Anastas & Beach, 2007; Clean Production Action, 2009a). The American Chemical Society's Green Chemistry Institute (GCI) Pharmaceutical Roundtable provides an opportunity for staff to exchange ideas and progress (e.g., Constable, et al., 2007; Manley, Anastas, & Cue, 2008). The Canadian Green Chemistry Network is affiliated to the GCI and devotes a lot of energy to pharmaceutical-related research. The emphasis in all these efforts is usually on saving money and reducing waste, and substitution efforts focus on solvents and surfactants, rather than APIs (e.g., Henderson, Jiménez-Gonzalez, & Constable, 2007). Nor is there an effort to consider other hazard categories when doing green chemistry work. ("You're the first person to ask me" how green chemistry practices account for ergonomic hazards and stressors of doing the job, said an influential leader in the field [Personal communication].)

5.3 Industry associations

Neither Rx&D, the association representing Canada's research-based pharmaceutical companies, nor the Canadian Generic Pharmaceutical Association appear to have publicly available OHS materials. The Quebec-based PharmaBio, a tri-partite organisation established to promote work in the pharmaceutical and biotechnology sector, has an OHS lab guide (PharmaBio, 2005). To the south, the Pharmaceutical Research and Manufacturers of America (PhRMA), which represents the non-generic U.S. drug and biotech companies, has no OHS documents on their website and their annual report considers safety only in terms of patients and products (Pharmaceutical Research and Manufacturers of America, 2008).

In the United Kingdom, the Association of the British Pharmaceutical Industry (ABPI) is the trade association for more than 70 companies. Its four OHS publications were developed more than 15 years ago, mostly in response to regulatory requirements. The publications are:

- *Guidelines on the control of radioactive substances in the pharmaceutical industry* (ABPI, 1996)
- *Guidelines on setting in-house occupational exposure limits for airborne therapeutic substances and their intermediates* (ABPI, 1995b)
- *Guidelines on the selection, use and maintenance of respiratory protective equipment in the pharmaceutical industry* (ABPI, 1995a)
- *Guidelines for chemical reaction hazard evaluation* (ABPI, 1989).

While these represented best practices at the time they were written, they are now outdated in the European context. Their occupation exposure limits document in particular has been superseded by more sophisticated control banding and green chemistry.

The Active Pharmaceutical Ingredients Committee (APIC) is a sector group within the European Chemical Industry Council (Cefic). Its purpose is to promote the use of "compliant APIs in medicinal products to ensure patient safety" (APIC, n.d., para 1) and, by representing API and

intermediate producers' interests, to influence regulatory efforts (APIC, n.d.). It maintains a list of industry best practices and position papers, one of which includes responses to regulatory efforts related to ICH Q8 (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). They cite an example of how taking a green chemistry approach introduces all kinds of difficulties, so that "APIs manufactured through an environmentally friendly process have great difficulty in gaining a market share in the EU" (APIC, 2007, p. 10). Nothing is said about worker health and safety (APIC, 2007).

There is, however, an indirect connection between APIC and OHS issues. In February 2009, its parent organisation—Cefic—became an official partner of the European Agency for Health & Safety at Work's Healthy Workplaces campaign on risk assessment (Cefic, 2008; Cefic, 2009). The campaign will be implemented through *prisme²*, a program for small and medium businesses, to be piloted in the Czech and Slovak Republics, Germany, Greece, Spain, and the U.K. The European Mine, Chemical & Energy Workers' Federation is one partner. The goals of *prisme²* are to:

- better understand the environment, health, and safety management needs of small businesses;
- commit leading companies to share best practices and involve their environmental and OHS specialists as *prisme2* "mentors";
- start regional Responsible Care[17] small business networking programs; and
- have trade unions engaged with work councils and employees as key actors in Responsible Care (Cefic, 2009).

European small businesses that are pharmaceutical industry suppliers may also be the object of another program. The Pharmaceutical Supply Chain Initiative (PSCI) is an effort by the major transnational companies[18] to deal with their suppliers. It is supposed to help them "operate in a manner consistent with industry expectations about labor, health and safety, environment, ethics and management systems" (PSCI, 2009a, para 1). An implementation guide and list of principles set out expected good business practices and behaviour (PSCI, 2007). OHS elements include information about chemical, physical, and biological hazards, as well as an overview of worker protection and information on process safety (PSCI, 2009b).

Abbott, one of the Canadian subsidiaries of a transnational pharmaceutical research company, developed supplier guidelines using the PSCI principles. The company expects suppliers to follow health and safety laws in these areas:

1. Worker protection: from exposure to chemical, biological, and physical hazards and physically demanding tasks;
2. Facilities, including living quarters and transportation vehicles;
3. Process safety: programs to prevent and respond to catastrophic releases of chemicals;

[17] The chemical industry's *Responsible Care* initiative started in Canada in 1985, arriving in Europe in the 1990s. It is coordinated by 53 national chemical industry associations—see www.responsiblecare.org. (Cefic)

[18] Companies involved so far are Abbott, Astra-Zeneca, Johnson & Johnson, Merck, Novartis, Pfizer, Roche and Schering-Plough. Activities are facilitated by Business for Social Responsibility (BSR). (www.pharmaceuticalsupplychain.org/about/index.php)

4. Emergency preparedness and response: for emergency situations affecting the workplace and any company-provided living quarters; and
5. Hazard Information: make available "safety information" for hazardous materials including pharmaceutical compounds and intermediate materials; educate, train, and protect workers from hazards (Abbott, n.d.).

6. Sex and gender considerations

In the last 15 years or so, much has been done to investigate women's occupational health issues. Researchers at CINBIOSE in Montreal are world-renowned for their efforts on this front. They have worked with Quebec unions, international NGOs and others to bring attention to hazards facing women and how the hazards are studied and addressed.

For the most part, however, discussion of hazards specific to women is absent in the literature, in news reports, and even in the workplace. Premji notes that

> (Hazards) found in women's jobs are often undramatic and diffuse, so the cause of some of these problems may not be obvious. In fact, women have more slowly-developing illnesses than men, and fewer accidents. This is significant because women may have left the workplace by the time they become ill. For instance, intoxications and other acute effects are more often found in jobs traditionally done by men in chemical factories, refineries and the like. It is also important to note that many of women's illnesses are multi-causal, and this also may make it difficult to establish a link to the workplace (Premji, n.d.).

In addition, a strict focus on differences between women and men can be misleading. Messing and Ostlin point out that "(D)ifferences within a sex are much greater than differences between the average values for each sex; there is great overlap between women and men for all important physical differences". However, "Women's and men's reproductive systems differ greatly. Women menstruate, become pregnant and nurse children, and these processes may be affected by workplace exposures. Men produce sperm, and this process is very sensitive to exposure to chemicals, vibration and radiation" (Messing & Ostlin, 2006).

Available evidence suggests that the validity of exposure estimates in epidemiology may be undermined by failure to consider possible gender differences in:

- job tasks within job titles;
- true exposure differences within otherwise similar jobs;
- differential validity of exposure estimates based on questionnaire tools or when cumulative exposure or exposure duration are used as surrogates for biologically relevant exposures (when exposure intensity is important); and
- the magnitude and direction of healthy worker effects[19] (Kennedy & Koehoorn, 2003, p. 582).

[19] "Healthy worker effect" refers to the observation that groups of workers are often healthier than the total population, or than that part of it to which they usually are compared in studies. This means that workers who were disabled, got sick, or were otherwise were affected by a job left that work, so that those left behind are the "healthy" ones.

The pharmaceutical industry preoccupation with toxicology and its underlying assumptions appears to influence how occupational exposure standards are set for workers in the sector; these standards are not necessarily appropriate for women.

Two of the original CINBIOSE researchers write that:

> .. it will be necessary to develop more sophisticated statistical and conceptual tools so as to understand more broadly how variables like sex and gender should be treated. .. (T)he meaning of human diversity for environmental and occupational health cannot be understood without an ecosystem approach that steps back and considers the multiple differences between the lived experience of men and women, and also the numerous similarities between the sexes (Messing & Mergler, 2006).

Finally, Messing and Stellman (2005) argue that mechanism is key and that there are five types of risks that could happen with "routine and insufficiently critical examination of sex and gender differences in health research" (p. 159):

1. There is a risk of false positives or false negatives, i.e., of discovering sex differences where none in fact exist, or of missing true effects.
2. There is a risk of overemphasizing sex differences in relation to other anatomical and physiological contributions to population variation.
3. Sex differences can be overemphasized if mean differences are reported but the population distributions are not.
4. There is a very large risk of confusion between sex and gender differences. In practice, sex and gender are not easy to unravel, given the multiple interactions between genes and environment in producing human health.
5. There is a risk of overemphasizing gender differences in relation to other effect modifiers in occupational health studies. Ethnicity, culture, social class, family type, and age are among the many other explanatory variables that may be involved in processes that produce health or illness (Messing & Stellman, 2005, pp. 159-160).

7. Conclusions

As in other work environments, a precautionary approach to hazards is the foundation of a healthy and safe pharmaceutical sector workplace and public health principles should guide responses for dealing with hazards. The best way to prevent problems is to eliminate the hazard or use substitution (choosing the safest or least toxic substance or process possible). Where this is not practicable, measures such as enclosure, which do not depend on individual behaviours, knowledge, or experience, can be used. Methods that rely on individual behaviours may be necessary in the short-term, but they are the least effective and potentially the most harmful.

The pharmaceutical industry is somewhat unique in that its workers handle and risk exposure to a range of materials intended to have biological effects. But the therapeutic effects desired for patients are not acceptable for those involved in producing pharmaceutical products (Binks, 2003; Teichman, Fleming Fallon, & Brandt-Rauf, 1988). While health and safety concerns are important in all phases of the continuum of pharmaceutical product production, use, and waste disposal, occupational health and safety issues in this sector have not received equal attention. Although large pharmaceutical companies seem to have more comprehensive health and safety

programs than most employers, largely because of non-OHS regulatory requirements and in-house OHS departments, their rationale for action is often economic efficiency and producing a safe end product, rather than the health and safety of their workers. When it comes to OHS issues, they tend to emphasis personal rather than company responsibility (as, for example, in behaviour-based safety programs).

Large pharmaceutical companies have done innovative work to classify chemical and biological hazards found in their plants and to develop methods to control exposures using a categorisation system known as control banding. While this method can speed up problem-solving activities, it is not based on efforts to substitute less hazardous materials—especially for APIs—and does not question the use or development of a substance before its hazards are known. Green chemistry efforts, which could address substitution issues, are rarely applied to APIs by the industry. While there is much attention in the literature and reports to the chemicals used, produced or present in drug R&D and production facilities, we still know very little about the consequences of exposure to most of them or of their interactions with other hazards.

In particular, the hazards posed by multiple exposures need careful consideration. A worker whose immune system is compromised by a stressful work environment, and whose workplace is not well-designed ergonomically, may well suffer more harm from exposure to toxic chemicals than someone whose only exposure is to the chemical hazard. As well, multiple chemical and biologic exposures, and repeated or long-term exposure must be considered.

Further, it seems reasonable to assume that chemical-related health effects of working in the pharmaceutical sector, particularly long-term effects, are likely under-reported and under-estimated. Other hazards (e.g., ergonomic design and stressors) are reported at higher rates in internal company systems, but are rarely discussed in the public literature (grey or otherwise). For female pharmaceutical workers, the lack of gender/sex analysis and information makes it unclear whether the latter category of hazards actually are more common in their work—as they are for women in other sectors—or whether chemical and biological hazards are more important factors for their health and safety.

The prevailing quantitative risk assessment approach to chemical management by Canada's OHS and environment laws and government authorities—including the cost-benefit aspects that are often hidden in discussions—is doing little to prevent work-related ill-health, injuries, diseases, and deaths among pharmaceutical workers. Given the more protective policies that have been and will be used in the European Union, implementation of global harmonization initiatives should have a positive impact on occupational health in Canada. The Nordic countries, in particular, offer useful examples of occupational health practices in their policies, as do the use of the precautionary principle and substitution requirements in the REACH program.

8. Recommendations

1. In terms of public policy, OHS tends to be overshadowed by environmental health concerns, both inside and outside pharmaceutical companies. As Joel Tickner and his colleagues argue in their work on sustainable chemistry, it is important that occupational health be integrated with protection of consumer and environmental health. They call for multi-agency approaches to chemicals management to avoid piecemeal, uncoordinated, and often

opposing efforts (Tickner, Geiser, K & Coffin, 2005). In the Canadian pharmaceutical industry context, this could mean that health and safety hazards in this sector would be more effectively prevented if Health Canada integrated occupational health and safety considerations into various programs and regulations, such as, for example, the Chemical Management Plans required under CEPA.

2. An international coalition of national and international public health and policy, environmental and trade union organisations has called for strong, comprehensive regulatory oversight at all levels of nanotechnology and its products (Nanoaction, 2007). Their demands include approaches that can be used for any hazard:
   - A precautionary foundation: Product manufacturers and distributors must bear the burden of proof to demonstrate their products are healthy and safe; there should be no market approval if there is no independent health and safety data review.
   - Mandatory nano-specific regulations: Nano-materials should be classified as new substances and subject to nano-specific oversight. Voluntary initiatives are not sufficient.
   - Health and safety of the public and workers: The prevention of exposure to nano-materials that have not been proven safe must be undertaken to protect the public and workers.
   - Environmental protection: A full life-cycle analysis of environmental impacts must be completed prior to commercialization.
   - Transparency: All nano-products must be labelled and safety data made publicly available.
   - Public participation: There must be open, meaningful, and full public participation at every level.
   - Inclusion of broader impacts: Nanotechnology's wide-ranging effects, including ethical and social impacts, must be considered.
   - Manufacturer liability: Nano-industries must be accountable for liabilities incurred from their products (Nanoaction, 2007).

It is recommended that Health Canada study these recommendations and consider Canada's role in regulatory oversight of these issues.

3. Given the upcoming implementation of the Registration, Evaluation, Authorisation and Restriction of Chemical substances regulation (REACH) in Canada, the steps large pharmaceutical companies are currently taking to comply with EU rules (where REACH is already in effect) and how these practices could be applied in Canadian plants, whatever their size, should be examined. Particular attention to requirements about reproductive and genotoxic substances, as well as to carcinogens and mutagens is needed.

4. It can be expected that global harmonization will affect MSDSs produced and used in Canada, especially those for APIs, intermediates and chemicals used in pharmaceutical R&D and production. The impact of global harmonization of MSDSs should be examined.

5. *The green screen for safer chemicals* (CPA, 2009b) in pharmaceutical settings should be evaluated. The "green screen" is a "benchmarking tool that assesses a chemical's hazard with the intent to guide decision-making toward the use of the least hazardous options via a process of informed substitution" (CPA, 2009b, p. 1).

Suggested further reading

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Appendix 1

Examples of reported chemical hazards and effects related to research lab and/or pharmaceutical lab and production work

1. Chemicals used/produced (general)

Acetylene
Acridine
Allyl alcohol
Ammonia
Ammonium hydroxide
Antimony and compounds
Arsenic
Benzyl chloride
Bromine
Chloroform
Cobalt and compounds
Corticosteroids
Cytotoxic agents (anti-neoplastic drugs)
1,2-Dibromomethane
1,2-Dichloroethylene
Dichoromethane
Dimethylaniline
Ethyl ether
Ethyl chloride
Ethylene chlorohydrin
Ethylene glycol dinitrate
Ethylenediamine
Extraction procedures
Fermentation and extraction process proteins
Fluorocarbons
Hexamethylenetetramine
Hydrazine and its derivatives
Hydrogen bromide
Hydroquinone
Magnesium and compounds
Manganese and compounds
Mercaptans
Molybdenum and compounds
n,n-Dimethylformamide
n-Butylamine
Nitroglycerin
Oral contraceptives
Phosgene
Picric acid
Platinum and compounds
Propyl alcohol
Pyridine
Silver and compounds
Sodium bicarbonate
Sodium hydroxide
Sulphur chloride
Tetrachloroethylene (perchloroethylene)
Toluene
Trichloroethylene
Turpentine

2. Chemical used/produced (process)

2.1 Reagents

Cyanogen bromide
Dimethyl sulphate
Dimethyl sulphoxide
Ethylenediamine
Formaldehyde
Glacial acetic acid
Glutaraldehyde
Hydrazine
Hydrochloric acid
Hydrofluoric acid
Isoamyl alcohol
Phosphoric acid
Sulphuric acid
Trichloroacetic acid

2.2 Gel electrophoresis

n,n-Methylene-bisacrylamide
ammonium persulphate
Ethidium bromide
n,n,n,n-Tetramethylethylenediamine
tris-acetate-EDTA

2.3 High pressure liquid chromatography work

Acetic anhydride
Acetonitrile
Ammonium hydroxide
Dimethylaminopyridine
Dimethylformamide
Ethanolamine
Ethyl acetate
n-Hexane
Methanol
Methylene chloride
n-Methylpyrrolidinone
Tetrahydrofuran
Triethylamine
Trifluoracetic acid

2.4 Histology work

Alcohols
Formaldehyde
Jsothiazolinones
Paraffin
Pyridine
Toluene
Xylene

2.5 Organic dust (dependant on the biologic product)

Aspergillus
Bacillus subtilis
Penicillium
Trypsin

Source: Key, Henschel, Butler, Ligo & Tabershaw, 1977; Klees & Joines, 1997; Naumann & Sargent, 1997.

Solvents used in primary pharmaceutical manufacturing

Solvent[20]	**Process(es)**[21]		
Acetone	C	F	B
Acetonitrile	C	F	B
Ammonia (aqueous)	C	F	B
n-Amyl acetate	C	F	B
Amy alcohol	C	F	B
Aniline	C		
Benzene	C		
2-butanone (MEK)	C		
n-Butyl acetate	C	F	
n-Butyl alcohol	C	F	B
Chlorobenzene	C		
Chloroform	C	F	B
Choromethane	C		
Cyanide	C		
Cyclohexane	C		
o-Dichlorobenzene	C		

[20] The names used are those in the original document. The chemicals may have other names but these are usually the most common ones. For information about their hazards, check the New Jersey Department of Health (www.state.nj.us/health/eoh/rtkweb/rtkhsfs.htm) or the Canadian Centre for Occupational Health and Safety (www.ccohs.ca) or the National Library of Medicine's Chemical Information database (http://sis.nlm.nih.gov/chemical.html).

[21] C = chemical synthesis, F = fermentation, B = biological or natural extraction

Solvent	Process(es)		
1,2-Dichlorobenzene	C		
1,2-Dichloroethane			B
Diethylamine	C		B
Diethyl ether	C		B
n,n-Dimethyl acetamide	C		
Diethylamine	C		
n-Dimethylaniline	C		
n,n-Dimethylformamide	C	F	B
Dimethyl sulfoxide	C		B
1,4-Dioxane	C		B
Ethanol	C	F	B
Ethyl acetate	C	F	B
Ethylene glycol	C		
Formaldehyde	C		
Formamide	C		
Furfural	C		
n-Heptane	C	F	B
n-Hexane	C	F	B
Isobutyraldehyde	C		
Isopropanol	C	F	B
Isopropyl acetate	C	F	B
Isopropyl ether	C		B
Methanol	C	F	B
Methylamine	C		
Methyl cellulose	C	F	
Methylene chloride	C	F	B
Methyl formate	C		
Methyl isobutyl ketone (MiBK)	C	F	
2-Methylpyridine	C		
Petroleum naphtha	C	F	B
Phenol	C	F	B
Polyethylene glycol 600	C		
n-Propanol	C		B
Pyridine	C		B
Tetrahydrofuran	C		B
Toluene	C	F	B
Trichlorofloromethane	C		
Triethylamine	C	F	
Xylenes			

Source: Tait, adapted from EPA, 1997.

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