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Health Hazards in the Pharmaceutical Industry

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Abstract

Extensive research is conducted to evaluate the safety and efficacy of candidate drugs prior to marketing and distribution, but few epidemiological studies have examined the occupational health of production workers who manufacture these drugs. This paper reviewed the occupational health research published during 1973-2014 regarding adverse health outcomes in pharmaceutical manufacturing workers. Most investigations were prompted by suspected disease clusters. Workers generally had a better mortality experience than their referent populations, but they experienced adverse health outcomes including cancer, endocrine dysfunction, cancer, and liver disease. However, most studies lacked detailed occupational exposure data, and they failed to identify the chemicals used in drug manufacture, including the active pharmaceutical ingredients (APIs). Integrated occupational health research is needed to evaluate exposures and long-term health outcomes among these workers. Since manufacturing operations are frequently outsourced to plants in Asia, this research could inform mitigation measures to protect production workers in this global industry.

Keywords: Active pharmaceutical ingredients; Occupational epidemiology; Mortality; Morbidity; Pharmaceutical industry

Introduction

Extensive research is conducted to evaluate the safety and efficacy of pharmaceutical drug candidates before regulatory entities, such as the US Food and Drug Administration (FDA), European Medicines Agency (EMA), or Japanese Ministry of Health, Labor and Welfare (MHLW), authorize the marketing of new drugs and additional indications of approved drugs. While the health status of chemical workers who manufacture non-pharmaceutical chemicals has been extensively studied, relatively few occupational studies have examined the health status of pharmaceutical production workers. The mortality and morbidity experience of pharmaceutical production workers has been previously discussed in three reviews [1-3].

Both Harrington and Teichman et al. reported an excess in cancer mortality and in the risk of endocrine dysfunction in pharmaceutical workers [1,2]. Teichman et al. also reported an increased risk of reproductive failure and respiratory allergies in pharmaceutical workers. Heron and Pickering noted that few industry studies have been published and that there is limited empirical evidence of an excess in morbidity and mortality related to occupational exposure among pharmaceutical production workers [3]. At least five studies have been published since that review by Heron and Pickering [4-7]. To our knowledge, there has been no published review to update the health risks associated with the manufacture of pharmaceutical products since the review by Heron and Pickering over a decade ago. The aim of this paper is to provide a comprehensive review of the literature on the adverse health effects associated with occupational exposure in pharmaceutical manufacturing workers from 1973 to 2014.

Methods

We conducted a literature search using OVID, PubMed, and Science Direct databases to find any journal articles published in the English language from 1973 to 2014. In order to identify relevant articles in the search, the following key words were included "pharmaceutical industry, drug industry, occupational health, occupational exposure, occupational disease, mortality, case-control study, cohort study" to identify appropriate articles. We then classified the results from the literature search by broad categories of study outcomes (mortality, cancer, liver disease, hormonal disorders, and allergic disease) and by study design (historical cohort, case-control, cross-sectional study, or case report). We also compiled a listing of case reports of adverse health effects in pharmaceutical workers, though this list was not exhaustive. These reports documented allergic sensitization from exposure to active pharmaceutical ingredients (APIs) or intermediates of APIs. We also supplemented these case reports with cross-sectional studies by the National Institute for Occupational Safety and Health (NIOSH) that had been published following inspections of pharmaceutical plants.

This review is a Type I, qualitative assessment, of the extant research on the occupational health of pharmaceutical workers given the disparate methods and absence of chemical exposure data [8]. No meta-analysis was conducted. An overview of the chemical exposure and industrial hygiene methods to reduce occupational exposures is provided elsewhere (Dolan DG, Gathuru IM, Buchanich JM, Marsh GM, unpublished manuscript).

Results

Mortality studies

Only seven studies have been published regarding the mortality experience of pharmaceutical workers (Table 1) [4-6,9-12]. All these studies were historical cohort studies except for the proportionate mortality study by Thomas and Decoufle.

The earliest mortality study by Thomas and Decoufle compared the cause-specific mortality experience of 826 white pharmaceutical plant employees and 249 sales representatives employed at a large US pharmaceutical firm between 1954 and 1976 [12]. They were compared to the general US population. Sales personnel had a similar mortality experience as the US population except for a deficit in violent deaths.

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Reference	Study design	Effect measure	Population	Findings	Comments
Thomas and Decoufle, 1979	Proportional mortality	PMR	826 plant workers and 249 sales personnel in the US followed during 1954-1976. Mortality compared to total US population.	The mortality experience of sales personnel similar to the US population except for a deficit in violent deaths. Plant workers had a higher total cancer mortality (PMR = 1.24-1.26) and suicides (PMR = 1.55-2.33) than the US population. Sex differences were also evident. Men had a mortality excess due to cancers of the skin, colon, kidney, brain and central nervous system. Women had an excess in cancers of the breast and respiratory system. Excesses were not confined at any given occupation group.	Plant workers and sales personnel had different mortality experiences. Site-specific mortality rates differed by sex. Occupational exposure was unrelated to cancer mortality. No APIs or process chemicals were identified.
Baker et al., 1986	Retrospective mortality	OR	672 workers in a British company who died in 1973-1981 and mortality was compared to the 1978 standard British population and to internal controls.	Excess pneumonia and cancer deaths evident. Risk of pneumonia deaths was elevated (OR = 1.41-1.68). Men had an elevated total mortality risk (OR = 1.71) of "other" cancers while women had an elevated risk of breast cancer (OR = 2.90) and cervical cancer (OR = 3.64). Comparisons using internal controls showed that the risk associated with "other" cancers in men was elevated (OR = 1.62, p = 0.06).	The follow-up period was short. The number of controls for the internal comparisons was small. There was a possible occupational risk associated with cancers of other sites among men. No APIs or process chemicals were identified.
Harrington and Goldblatt., 1986	Historical cohort	SMR	Two cohorts of 1,472 and 2,102 workers based on 1961 and 1971 census data from England and Wales, respectively, were followed until 1981. Comparisons were made to the standard population in England and Wales. Comparisons of chemical industry groups.	1961 and 1971 cohorts in both sexes showed a deficit in overall mortality. Both male cohorts had deficits in deaths due to all causes (SMR = 0.77- 0.81) and circulatory disease (SMR = 0.76-0.83). The 1961 male cohort had a deficit in all respiratory disease mortality (SMR = 0.63) while the 1961 female cohort had a deficit in all-cause mortality (SMR = 0.50). Deficits also evident in other industry groupings. Mortality excesses were not confined to any specific industry grouping.	Mortality excesses in industry comparisons were small. No evidence that mortality risk was related to employment in the pharmaceutical industry. No APIs or process chemicals were identified.
Edling et al., 1995	Historical cohort	SMR	Cohort of 3,514 plant workers 1960-1990 compared to Swedish Cancer Registry.	The cohort had fewer than expected deaths from all causes combined (SMR = 0.70). None of the cause-specific deaths were elevated.	This cohort had a lower mortality experience than the general population. No APIs or process chemicals identified.
Dolan et al., 2004	Historical cohort	SMR	1,958 workers employed during 1950-1999 at a US plant and their mortality compared to the US and local standard populations.	There was a deficit in deaths due to all causes (SMR = 0.76) and heart disease (SMR = 0.76) relative to the US population. Independent of sex, age, and job class, there was no mortality excess.	This cohort had a better all-cause and heart disease mortality experience than the general population. No APIs or process chemicals were identified.
Marsh et al., 2005	Historical cohort	SMR	1,999 workers employed during 1970-1996 and followed through 2004. Their mortality was compared to local and US standard populations. Mortality among men due to respiratory system cancers (RSC) and lymphatic-hematopoietic tissue cancers (LHTC) especially non-Hodgkin's lymphoma (NHL) was also examined by work history.	Overall deficit in mortality due to all causes and heart disease (SMR = 0.76 for both). An almost 3-5-fold mortality excess related to work history was observed. Male workers with potential plant exposure had excesses in RSC deaths and LHTC deaths especially NHL. Tobacco smoking attenuated the RSC mortality risk. LHTC mortality risk increased with increasing levels of solvent exposure.	Cohort had a better mortality experience than US and local populations. RSC mortality excess may be have partly explained by tobacco smoking. LHTC mortality excess was probably related to occupational factors. No APIs or process chemicals were identified.
Youk et al., 2009	Historical cohort; Nested case-Control study	SMR (Cohort study) and OR (case-control study)	Male workers with some full-time employment during 1970-1996 and followed through 2004. Their mortality was compared to local and US standard populations.	Subjects with potential plant exposure had no elevated RSC risk and a statistically significant LHTC excess. The nested case-control study found many RSC risks decreased upon adjustment for smoking. LHTC risks rose with increasing levels of exposure to dimethylformamide (DMF), but the specific API manufactured using DMF was unknown.	Smoking explained some of the RSC mortality excesses, but occupational factors were implicated in the LHTC mortality excess.

Table 1: Mortality studies of pharmaceutical production workers.

In contrast, both sexes of plant workers had a significantly higher all-cancer mortality (PMR = 1.24 in men and PMR = 1.26 in women) and suicide deaths (1.55 in men and 2.33 in women) than the U.S. population. Site-specific cancer mortality excesses among plant workers differed by sex. Males had statistically significant excesses in cancers of the colon, brain and central nervous system, and kidney. Females had statistically significant excesses in cancers of the breast cancer, leukemia and respiratory cancer. However, none of the site-specific cancer mortality excesses were confined to any specific chemical or to any one of the three occupational groups among the plant employees (i.e., production, maintenance/ engineering, or administrative, clerical and miscellaneous). Thus, the authors concluded that cancer mortality excesses observed in this cohort may have been related to unknown occupational factors.

Baker et al. conducted a historical cohort study of 672 pharmaceutical workers who were employed at a British company and who had died between 1973 and 1981 [9]. They compared the mortality experience of these workers to two reference groups: the general population of England in 1978 and an internal group of pharmaceutical workers. There was a statistically significant higher rate of pneumonia-related mortality in both sexes than in the general population (OR in men = 1.41; 95% CI: 1.00-2.00 and OR in women = 1.68; 95% CI: 1.01-2.79), but cancer mortality rates differed between the sexes. Compared to the general British population, male workers had significantly elevated mortality excess for cancers of 'other sites' (OR = 1.71; 95% CI: 1.18-2.48) with the largest number of 39 deaths occurring in either the pancreas (n = 8) or urinary tract (n = 8). Female workers had statistically significant excess cancer mortality for all sites, breast, and cervix compared to the general population. While there was limited

work history on this cohort, comparison of mortality experiences with internal controls among men showed a borderline significant result in the odds of cancers of 'other sites' (OR = 1.62; p = 0.06) after controlling for age, exposure type, and duration of employment. None of the other mortality excesses among men or women remained statistically significant after comparisons with internal controls. The authors concluded that there was a possible occupational risk associated with "other site" cancers among men.

Harrington and Goldblatt conducted a cross-sectional study to examine the mortality experience of a British cohort of 1472 pharmaceutical workers in the 1961 census and 2102 workers in the 1971 census [11]. Both cohorts were followed through the end of 1981 and their mortality experience was compared to that of the general British population. There was an overall deficit in causes of mortality in the 1961 and 1971 cohorts of both sexes, but most of these deficits were not statistically significant. However, both male cohorts had statistically significant deficits in mortality due to all causes (SMR = 0.77- 0.81) and circulatory disease (SMR = 0.76-0.83). The 1961 male cohort had a statistically significant deficit in all respiratory disease mortality (SMR = 0.63, 41 observed deaths versus 65.5 expected deaths) while the 1961 female cohort had a statistically significant deficit in all-cause mortality (SMR = 0.50, 10 observed deaths versus 20.1 expected deaths). Additional analysis by industry generally showed a deficit in mortality for most causes among workers employed in various chemical industries. The authors concluded that there was no evidence of a mortality risk associated with employment in the pharmaceutical industry [11].

Edling et al. conducted a historical cohort study following the report of a suspected cluster of cancers (brain, pancreas, stomach, and lung) in six of the 120 workers employed at a Swedish pharmaceutical plant [10]. The study focused on possible exposure to biological, chemical or pharmacological agents among workers who had been employed for at least six months from 1960 through 1989. Overall, the total deaths were fewer than expected in this cohort (92 observed versus 131 expected). Similarly, there was a mortality deficit for most other causes. There was no significant increase in any cause of death. Also, these investigators examined the cancer incidence of workers in this study (see 3.2.1 for details). No APIs or process chemicals were identified in this study.

Dolan et al. conducted a historical cohort study to examine the mortality experience of a cohort of plant workers employed from 1950 to 1999 at a US pharmaceutical company in response to workers' concerns about their health [4]. Out of the 1958 workers included in the cohort, there were 384 deaths. The pharmaceutical workers had a lower mortality due to all causes (SMR = 0.76; 95% CI: 0.69 - 0.84) and all heart disease (SMR = 0.76; 95% CI: 0.64-0.90) relative to the local population. Similar results were obtained with comparisons of mortality with the US population. There was no evidence of any excess mortality risk after adjusting for age and sex, or job classification. The authors concluded that there was no evidence of any relationship between occupational exposure and mortality.

In response to community concerns regarding an increase in countywide cancer rates, Marsh et al. conducted a historical cohort study to examine the mortality experience of 1999 workers at a US pharmaceutical production plant with some full-time employment during the period between 1970 and 1996 [5]. Their mortality experience between 1970 and 2000 was compared to US and local county mortality rates. There was a statistically significant deficit in the deaths due to all causes (SMR = 67; 95% CI: 56-81) and due to all heart disease (SMR = 59; 95% CI: 39-86) than the US population. Similar results were obtained in comparisons with the local county population. Though not statistically significant, there was a deficit in the total cancer-mortality. Male workers with potential plant exposure had excesses in deaths from respiratory system cancers (RSC) and from all lymphatic-hematopoietic tissue cancers (LHTC) especially non-Hodgkin's lymphoma (NHL). The LHTC and NHL mortality risk was almost three to seven-fold higher than that observed in the local population after adjusting for time-related factors (i.e., age, employment period, employment duration, and time since first employment). The extensive assessment of these solvents and work history failed to show a consistent pattern with any given solvent. However, no APIs were identified in this study. It is possible that tobacco smoking may have partly contributed to these excesses, but information could not be ascertained for these workers. Thus, the authors concluded that the smoking could partly explain some of mortality excess associated with RSC and that occupational factors may have accounted for the mortality excess associated with LHTC.

Youk et al. updated the cohort mortality study by Marsh et al. through 2004 [6]. This updated study specifically examined the RSC and LHTC mortality excesses evident among the 1466 full-time male workers. A nested case-control study was also conducted to elucidate the occupational factors associated with these LHTC and RSC mortality excesses. Many RSC risks were attenuated after adjusting for smoking history. While, LHTC risks rose with increasing levels of average exposure to dimethylformamide (DMF), the specific APIs that were synthesized using DMF as a solvent were unknown. The authors concluded that smoking explained some of the excess mortality associated with RSC and that occupational factors may have been implicated in the excess LHTC mortality risk.

Morbidity studies

Cancer: Three studies have examined the cancer morbidity of production workers [10,13,14], and their findings are summarized in Table 2. Two of these studies were historical cohort studies [10,14], and third one was a cancer registry that used PCIR estimates [13].

Hall and Rosenman examined cancer incidence data from the New Jersey State Cancer Registry to determine the association between workplace exposures and cancer incidence in a cancer registry [13]. Industry-specific proportional cancer incidence ratios (PCIRs) were computed by race and sex with a focus on manufacturing and construction industries in the US. The study focused on cancers that involved three or more cases. Among the 433 pharmaceutical workers identified in the registry, black females (PCIR = 164, $p < 0.05$) had an elevated risk of breast cancer while white males had an elevated risk of acute granulocytic leukemia (PCIR = 305, $p < 0.05$). The risk of granulocytic leukemia among white blue-collar workers in the pharmaceutical industry was higher than among all white, blue-collar workers (PCIR=374, $p < 0.05$). There was an overall elevated cancer risk among white males and black females. However, at least 32% of cases were lacking occupation and industry information. Therefore, the association between cancer risk and specific workplace exposures could not be determined in this study.

Hansen et al. conducted a historical cohort study at a Danish pharmaceutical plant that manufactured insulin, antibiotics, enzymes, and sex hormones to investigate the cancer incidence among 10,889 workers employed during 1964-1988 [14]. Using the national Danish registry, standardized incidence ratios (SIR) were between the cohort and the Danish population. Male workers had a similar risk of total cancer as the general population, while female workers had a 16% higher total cancer risk than the general population. Male workers had

Reference	Study design	Effect measure	Population	Findings	Comments
Hall and Rosenman, 1991	Registry	PCIR	Population-based cancer registry in New Jersey (US) during 1979-1984. Rates were compared by sex, race and occupation/ industry.	Black females had an elevated risk of breast cancer (PCIR = 164, $p < 0.05$). White males had an increased risk of acute granulocytic leukemia (PCIR = 305, $p < 0.05$), and risk was even higher among white blue-collar workers. At least 32% of cases had missing occupation/industry information.	Elevated risk of cancer in black females and white males in the pharmaceutical industry. Relation of workplace exposure with cancer risk was unknown.
Hansen et al., 1994	Historical cohort	SIR	Cohort of 10,889 workers employed between 1964-1988 involved in production of insulin, sex hormones, enzymes and antibiotics at a Danish plant. Cohort followed from 1964-1989 and compared to the Danish standard population.	Cancer morbidity risk in men was similar to the general population (SIR = 0.95) except for a higher risk for intestinal cancer (SIR = 5.4) and a lower risk of testicular cancer (SIR = 0.2). Women had an overall elevated risk of all cancers (SIR = 1.2), breast cancer (SIR = 1.5), larynx (SIR = 4.3), and pancreatic cancer (SIR = 2.0). The breast cancer excess was highest in women who started working in their thirties and continued employment for 1-9 years at the plant.	No consistent evidence of any relationship between occupational exposure to insulin and estrogens and the risk of breast cancer in women.
Edling et al., 1995	Historical cohort	SIR	Cohort of 3,514 plant workers 1960-1990 compared to Swedish Cancer Registry. County population was the reference except peritoneal cancer estimates which were based on national rates.	No significant increase in the all-cancer incidence or in any of the suspected cluster of brain, pancreatic, stomach, and lung cancer, independent of disease latency. However, there was an elevated risk of urothelial cancer among workers with high exposures after adjusting for disease latency (SIR = 3.3). All 7 cases had chemical, pharmaceutical or biological exposures, but no common exposure was identified among these cases. 6 of 7 seven cases had a history of smoking.	No common occupational exposure was identified. Tobacco smoking accounted for some of the excess in urothelial cancer. However, no specific chemical exposure was associated with urothelial cancer.

Table 2: Cancer morbidity.

a lower risk of testicular cancer (SIR = 0.2; 95% CI: 0.0-0.8) and had a higher risk of intestinal cancer (SIR = 5.4; 95% CI: 1.5-14.0) than the general population. Female workers had a lower risk of cervical cancer (SIR = 0.4; 95% CI: 0.2-0.8) than the general population. However, females had an excess risk in pancreatic cancer (SIR = 2.0; 95% CI: 1.0-3.7), laryngeal cancer (SIR = 4.3; 95% CI: 1.2-11.0), and breast cancer (SIR = 1.5; 95% CI: 1.2-1.8). The breast cancer excess was mostly observed among women who had begun employment at the plant during ages 30-39. Also, there were two cases of male breast cancer among long-term employees while a third case was diagnosed after the closing date of the study. This finding suggested that occupational exposure to estrogens and insulin may have played a role in the incidence of breast cases in this cohort. The authors concluded that the overall excess in breast cancer in this cohort of workers could not be exclusively attributed to occupational factors without more precise data on occupational exposure.

Edling et al. conducted a historical cohort study to investigate the cancer incidence in a cohort of 3514 Swedish pharmaceutical workers who had been employed for at least six months during 1960-1989 [10]. Occupational exposure was deemed to be high among workers who used biological, chemical/radiological, or pharmacological agents in their job, and it was deemed to be low among those workers with indirect exposure. The mortality experience of this cohort has been previously discussed in Section 3.1 regarding mortality studies. There was no statistically significant increase in the all-cancer incidence. Independent of a 10-year latency period, there was no excess in any of the malignancies observed in the putative cluster of brain, pancreatic, stomach, and lung cancer. However, workers with high exposure experienced a higher risk of urothelial cancer than the local population after adjusting for disease latency (SIR = 3.3, 95% CI: 1.2-7.3). All seven cases of urothelial cancer had chemical, pharmaceutical or biological exposures, but there was no common exposure identified among these cases. Six of the seven cases had a history of smoking. The authors concluded that smoking alone could not explain the entire elevated incidence of urothelial tumors.

Liver disease: Two studies have examined the risk of liver disease among pharmaceutical workers [15,16]. These studies are summarized in Table 3. Heinemann et al. launched an international, hospital-based case-control study during 1990-1996 to investigate the relationship between liver cancer and occupational exposure among 317 cases and 1789 controls [16]. Cases were matched by age within a five-year range to four hospital or community controls. Occupational exposure was based on self-reported lifetime work history by industry, self-reported exposure to specific chemicals, or proxy measure of occupational exposure to 50 chemicals using a job-exposure matrix. There were only eight cases and 23 controls with a history of employment in the pharmaceutical industry, and it is unknown whether any of these workers were involved in the manufacturing process of pharmaceutical products. Pharmaceutical workers had a greater than two-fold risk of liver disease (OR = 2.44, 95% CI: 0.77-7.73), but this risk was not statistically significant after adjusting for age, smoking, drinking, oral contraceptive use, and medical history of hepatitis. The relationship between occupational factors and liver cancer was inconsistent. The authors concluded that there was insufficient evidence of a relationship between occupational factors and liver cancer among pharmaceutical workers.

Tomei et al. conducted a cross-sectional study of liver function in 40 pharmaceutical workers aged 21-56 years who took part in the entire production cycle at a pharmaceutical plant that manufactured xenobiotics (antihistamines, antibiotics, disinfectants, preserving agents and cortisone) in Italy [15]. There were 86 controls who were unexposed to hepatotoxic substances and who were employed in various occupations. Liver function was evaluated based on biochemical indices of liver toxicity. Potential risk factors for hepatic pathology including alcohol consumption, family and medical history were ascertained by questionnaire. The authors observed that while both groups of workers had similar non-occupational risk factors including socio-environmental background; exposed workers had higher risk of having abnormal liver function tests than unexposed workers (45% versus 15%, $p < 0.05$). Although the potential confounding role of alcohol intake in this study was not examined, the authors concluded

Reference	Study design	Effect measure	Population	Findings	Comments
Heinemann et al., 2000	Hospital-based, case-control	Odds Ratio	1:4 matching with 317 cases with hepatocellular carcinoma (HCC) and 1789 controls in six European countries. 8 cases and 23 controls employed in the pharmaceutical industry.	An elevated but nonsignificant increase in the risk of HCC among pharmaceutical industry workers (OR = 2.4, p > 0.05). No evidence of an elevated risk of HCC with increasing duration of exposure. There was an inconsistent relationship between HCC and occupational factors (industry, exposure and exposure level).	Unclear if the cases in pharmaceutical industry (n = 8) were involved in manufacturing processes. Occupational factors were not associated with HCC in the study.
Tomei et al., 1995	Cross-sectional	N/A	40 cases and 86 controls in Italian pharmaceutical plant that manufactured xenobiotics	No occupational factors were similar between cases and controls. Compared to controls, cases had almost a 3-fold risk of having abnormal liver function tests (15.1% vs. 45.0%) and a greater than 5-fold risk of elevated liver enzymes than controls (5.8% vs. 37.5% for ALT and 4.6% vs. 17.5% for AST).	Multiple, low-level exposure to xenobiotics was associated with liver toxicity. The possible role of alcohol intake as a confounder was not examined. No specific APIs were identified.

Table 3: Liver disease.

that occupational exposure to low doses of multiple xenobiotics was associated with the increased risk of liver toxicity observed among production workers.

Reproductive dysfunction: Studies on reproductive dysfunction have focused on exposure to organic solvents [17] and to estrogen [18-22]. These studies are summarized in Table 4.

Organic solvent exposure: Taskinen et al. conducted a hospital-based, case control study to investigate spontaneous abortions among female workers employed at eight Finnish pharmaceutical factories during 1973-1980 [17]. The study examined occupational exposure to solvents (such as methylene chloride), estrogens, antineoplastic agents and carcinogens. The study group comprised women who had been employed for at least one week during their trimester of pregnancy. Each case with a spontaneous abortion during employment at the plant was matched to three controls who had a live birth during the same time period (n = 44 and n = 130, respectively). Spontaneous abortions were identified using the eighth revision of the International Classification of Diseases (ICD8) codes 643 and 645 while live births were identified using ICD8 codes 650-662. Clinicians who assessed occupational exposure during the first trimester were blinded to the case/control status of each woman. Cases had higher rates of exposure to solvents (such as methylene chloride), estrogens, antineoplastic agents and carcinogens than controls. Other health outcomes in mothers (e.g., infertility manifested as no exposed pregnancies or unrecognized pregnancy loss) or their offspring (e.g., malformations) were not evaluated. Spontaneous abortions were independently associated with continuous heavy lifting at work (OR = 5.7; 95% CI: 1.3-26.0), exposure to four or more solvents (OR = 3.5, 95% CI: 1.0-12.4), and estrogen (OR = 4.2, 95% CI: 1.0-18.2). The authors concluded that organic solvent exposure had an adverse effect on the pregnancy outcome in exposed female workers, independent of estrogen exposure and heavy lifting at work.

Estrogen exposure: Five studies investigated occupational exposure to sex hormones and the risk of reproductive dysfunction [18,20-23]. All of these studies were cross-sectional in design. While each study reported adverse effects at the time of evaluation, none of these studies evaluated any long-term sequelae of exposures (e.g., increased risk for cancer, infertility, birth defects).

Harrington et al. conducted a cross-sectional study to examine the association of estrogen exposure and *hyperestrogenism* in 55 employees (30 women and 25 men) who produced oral contraceptives at a pharmaceutical manufacturing facility in Puerto Rico [24]. Twelve (40%) women had a history of at least one episode of intermenstrual bleeding in the last 12 months, while 20% (n = 5) of the exposed men had a history of gynecomastia. Exposed females were matched by age and socioeconomic to 60 non-factory controls, and they had a significantly higher risk of clinical *hyperestrogenism* (RR = 4.26; 95% CI: 1.61-11.26) than their matched controls. It was concluded that the hyperestrogenic effects observed in male and female workers in the study were associated with occupational exposure to estrogens.

Shmunes and Burton led a cross-sectional study following a 1972 investigation by NIOSH that involved male production workers exposed to diethylstilbestrol (DES) in the US [20]. There were 23 instances of DES reaction in a team of eight workers, and this reaction included breast tenderness, gynecomastia, and periods of sexual impotence in some workers. The investigators used 24-hour urinary monitoring to assess DES exposure in the absence of a federal exposure limit standard or company occupational exposure limit for DES. All five full-time workers had increasing DES levels with days of exposure, and two became symptomatic after their urinary DES levels rose above 40 μg/ml. However, their DES levels dropped to 3.7 μg/ml or lower following six days of nonexposure after DES manufacturing was halted. There was insufficient ventilation and inadequate decontamination procedures at this plant. The authors concluded that DES exposure was associated with the feminizing symptoms observed in exposed male workers.

Willems conducted a cross-sectional study at a pharmaceutical plant in the Netherlands where more than 30 kinds of estrogens were manufactured [21]. The study involved 23 male production workers aged 24-58 who lacked a prior history of endocrine disorders. Manufacture of the estrogens took place in three separate sections, and these sections were labeled A, B, or C according to relative levels of exposure. Section B workers were considered to be at highest risk for exposure while section C workers were considered to be at lowest risk for exposure, although no exposure measurements were made. Exposed workers were matched to two unexposed workers by age and shiftwork. Workers in Section B (n = 7) had statistically significantly different sex hormone levels compared to non-exposed controls; no differences were found between subjects and controls in Sections A or C. However, the effect of these elevated hormone levels on male fertility and libido were not evaluated. Nevertheless, the symptoms of

Reference	Study design	Effect measure	Population	Findings	Comments
Organic solvents					
Taskinen et al., 1986	Hospital-based case-control	OR	44 cases with spontaneous abortions in eight Finnish pharmaceutical plants matched to 130 controls among women employed for at least one week during pregnancy	Cases had higher rates of exposure to organic solvents than controls. Solvent exposure was associated with increased risk for spontaneous abortions after adjusting for estrogen exposure and heavy lifting (OR = 4.2).	Exposure to organic solvents associated with increased risk of spontaneous abortions, independent of heavy lifting and estrogen.
Estrogen					
NIOSH, 1990	Case report	N/A	23 male workers involved in the manufacture of diethylstilbestrol (DES).	Workers were found to have breast tenderness and enlargement. Some workers also reported having periods of sexual impotence.	Hyperestrogenism evident in exposed male workers. Health effects are consistent with effects of this drug.
Harrington et al., 1978	Cross-sectional & matched case-control	OR	55 exposed workers (30 women and 25 men) at a factory where estrogens were formulated in Puerto Rico	Hyperestrogenism observed in 40% of exposed women and 20% of exposed men. Rates of inter-menstrual bleeding higher in the 30 exposed than in the 60 unexposed women (40% vs. 16.7%). Risk of hyperestrogenism was 4.3 times higher in exposed than in unexposed women.	Estrogen exposure may increase the risk of hyperestrogenism in exposed men and women. Health effects are consistent with effects of this class of drug.
Willems, 1981	Cross-sectional	N/A	23 male workers in a plant in the Netherlands involved in estrogen manufacture were matched to 2 controls by age and shiftwork.	The highest exposed workers (n = 7) had higher rates of abnormal hormone levels than unexposed workers. 5 of 6 workers with low male hormone levels belonged to the group with the highest exposure and they had abnormal hormone levels	Estrogen exposure was associated with the occurrence of abnormal hormone levels in men. Fertility, reproductive outcomes and libido were not evaluated. Health effects are consistent with effects of drug.
Estrogen exposure					
	Cross-sectional	N/A	40 workers (18 men and 22 postmenopausal women) involved in production of oral contraceptive pills	Estrogen levels and liver enzymes were significantly elevated among exposed workers of both sexes. Testosterone levels declined in exposed males compared to unexposed males. Higher estrogen levels among exposed workers were associated with an improved lipid profile but a prolonged bleeding time.	Occupational exposure to oral contraceptive pills had an adverse heath effect on exposed workers resulting in changes in an alteration in liver function and sex hormone levels.
Rao et al., 2003	Cross-sectional	Clinical findings, blood hormone levels	38 workers (11 in steroid processing, 16 in non-steroidal processing or frequent visitors of steroid processing area, and 11 unexposed)	Increased prevalence of clinical signs in symptoms of sex hormone exposure among sex steroid hormone manufacturing workers, and suppression of all blood levels of all sex hormones among these workers compared to other plant workers.	Industrial hygiene measurements supported the likelihood of high exposure levels to sex steroids. Suppression of endocrine function and disruption of reproductive function were evident in exposed workers.

Table 4: Reproductive outcomes by exposure.

hyperestrogenism in male workers were linked to estrogen.

Shamy et al. examined the biochemical changes associated with estrogen exposure during the manufacture of oral contraceptive medications at a plant in Egypt [23]. This study involved 18 male and 22 postmenopausal female workers involved in the manufacture of contraceptive pills and 34 females involved in the manufacture of contraceptive ampoules. A matched control group consisting of 19 males and 27 females was recruited from administrative departments at the plant. Estrogen levels and liver enzymes were significantly increased among exposed workers of both sexes. Male workers had significantly lower testosterone levels than male controls. Overall, there was an increase in the clotting time but an improvement in lipid profiles among exposed workers. It was concluded that occupational exposure to contraceptive medications was associated with the biochemical profile changes evident in exposed production workers.

Rao et al. investigated the health effects of sex steroids among workers at a pharmaceutical plant that manufactured contraceptive pills [22]. The study involved 38 workers who were classified into three groups by exposure to the sex steroids. The first group consisted of 11 workers (8 female and 3 male) in the area where steroids were manufactured (steroid group), and these workers had been exposed for a duration of 15 days to one year. The second group had 16 male workers who had been either been reassigned to a non-steroid manufacturing area after experiencing health problems in the steroid areas or who had visited the steroid processing area frequently (non-steroid group). This second group had been exposed for duration of 15 days to five months. The third group had 11 male workers in other areas of the plant who were unexposed (control group). It was estimated that the steroid and non-steroid groups had been exposed to airborne levels of steroids that were two to three orders of magnitude higher than daily medicinal doses. All exposed workers experienced various adverse effects. All eleven exposed women had menstrual problems. Among the 19 men with some exposure, 15 reported having loss of libido while 13 of the 16 men in the non-steroid group experienced a variety of breast problems including mastalgia and gynecomastia. However, most workers in the nonsteroid area became asymptomatic after their transfer from the steroid area. All exposed workers showed signs of suppressed levels of endogenous steroid hormones, but this effect were more pronounced in the steroid group than in the nonsteroid group.

However, there were no inferential statistics presented in this study. Nonetheless, the authors concluded that the high levels of airborne steroids were linked to the breast problems experienced by men and to the suppression of endocrine function and disruption of reproductive function experienced by both sexes.

Adrenal dysfunction: There are occupational data that suggest that occupational exposure to steroids during their production may lead to the suppression of adrenal function [25,26], but some corticosteroid exposure levels may not be high enough to cause adrenal dysfunction [27]. Findings regarding studies on adrenal dysfunction are displayed in Table 5. There was no longitudinal evaluation of the morbidity (e.g., cardiovascular, endocrine, or liver disease), or mortality experience of these workers.

Newton et al. conducted a cross-sectional study to investigate the relationship between occupational exposure to glucocorticoids and adrenocortical suppression in 12 production workers at a pharmaceutical plant in Scotland where the glucocorticoid betamethasone was manufactured [25]. This study was initiated after an index case was diagnosed with chronic adrenal insufficiency after 16 years of exposure to various products at the plant. The remaining 11 workers were asymptomatic except for facial swelling, a salient characteristic of absorption of glucocorticoids. In addition to the index case, two workers showed evidence of adrenal insufficiency.

In a second cross-sectional study, Newton et al. examined the effects of glucocorticoids on adrenal function by comparing 20 exposed workers to 19 unexposed workers after production controls had been initiated at the plant [26]. Workers involved in the production of glucocorticoids, either biologically active or inactive, had lower mean levels of cortisol than unexposed workers in this latter study. Both studies by Newton showed that occupational exposure to glucocorticoids may be related to the risk of adrenocortical dysfunction even in the absence of overt symptoms.

Phillips conducted a cross-sectional study of workers at a pharmaceutical plant in the United Kingdom where aerosols of beclomethasone dipropionate (BDP), an inhaled corticosteroid used to treat asthma, allergic rhinitis, and skin problems, was manufactured [27]. The author examined the health effects related to steroid exposure. Skin symptoms were evident among 68 workers exposed to glucocorticoids, but there was no evidence of suppression of adrenocortical function. Also, none of the workers had any evidence of respiratory allergic responses to the API or excipient compounds. Thus, the author concluded that levels of exposure to glucocorticoids may have been sufficient to cause allergic skin disorders but insufficient to suppress adrenocortical function.

Allergic disease: The preponderance of occupational health data has documented allergic sensitization involving the respiratory system or skin among pharmaceutical workers. Most of these data have been primarily documented in case reports. The most commonly reported allergic diseases have been occupational asthma (Table 6) and contact dermatitis (Table 7).

Occupational asthma: Occupational asthma (OA) is one of the leading causes of occupational lung diseases [28]. Several case reports and a few surveys demonstrate that OA may occur among production workers especially in the manufacture of antibiotics and enzymes.

Antibiotics: Thirteen case reports document inhalation of dust from antibiotics and the occurrence of OA in a total of 53 workers [29-40]. Only three case reports documented OA cases in three or more workers [29,32,40]. Most exposed workers developed symptoms within one year of exposure in seven of the 11 reports with data on latency [30-34,36-38]. The four reports documented a latency of 2 or more years [29,32,35,40]. Angulo et al. conducted a systematic review of 23 case reports in addition to the documentation of four OA cases. This review showed that the 21 of 37 (58.3%) cases developed symptoms within one year of exposure [29].

Enzymes: Four types of enzymes were found to be associated with 37 cases of OA documented in five investigations: papain [41,42], bromelain [41], pepsin [43], and lactase [44,45]. The majority of these OA cases occurred within 1½ years of exposure. Baur and Fruhmann reported that an index case exposed to bromelain developed OA after being exposed for 10 years. They evaluated six workers for sensitization to papain and identified two cases who had an unspecified latency period [41]. Twelve cases exposed to papain for 12-15 months were identified in a survey of 23 workers by Novey et al. [42]. Cartier documented a case who had been exposed to pepsin for 1½ years [43]. Two separate investigations implicated lactase in a total of 21 cases [44,45]. Laukannen et al. reported a case that developed OA within one year of exposure to lactase [44]. Lactase was also linked with OA in 20 workers out of 203 exposed workers surveyed by Muir et al. [45].

Opioid analgesics: There have been at 18 documented cases of OA that occurred after exposure to opioid analgesics [46-49]. All four investigations involved an exposure to morphine, but two of them reported exposure to other opioids such as codeine [48,49], dihydroxycodeine, oxycodone, and hydrocodone [48]. Overall, the

Reference	Study Design	Population	Findings	Comments
Newton et al., 1978	Case-report	12 production workers employed at a plant in England	All 12 workers with occupational exposure to glucocorticoids had facial swelling associated with facial contact with glucocorticoids.	Glucocorticoids increased risk of adrenocortical suppression in exposed workers. Health effects are consistent with this class of API.
Newton et al., 1982	Cross-Sectional Survey	28 production workers (20 exposed to active material and 8 exposed to inactive material) and 19 controls	20 workers showed gross adrenocortical suppression in those who worked in an area where concentration of glucocorticoids was high compared to workers who worked with inactive material or with no glucocorticoid.	Exposure to glucocorticoids (active or inactive) found to be associated with adrenocortical suppression. Health effects are consistent with this class of API
Phillips, 1982	Cross-Sectional Survey	102 men and women involved in production of glucocorticoid, beclomethasone	Skin reaction was the most frequent complaint (61.8%). No adrenocortical suppression was evident in these workers.	Glucocorticoid levels of exposure appeared not to be high enough for adrenocortical suppression.

Table 5 Adrenocortical suppression.

Reference	Investigation	Location	Number of cases of cases	Product class/name	LatenL Latency period for sensitization
Antibiotics					
Angulo et al., 2011	Case report	UK	3	Penicillin, amoxicillin	19 years (n=1) 2 years (n=1) 27 years (n=2)
			1	Erythromycin	2 years
Choi et al., 2009	Case report	S. Korea	1	Vancomycin	5 months
Coutts et al., 1981	Case report	UK	2	Cephalosporin	1 month (n=1) NA for 2nd case
Davies et al., 1974	Case report	UK	4	Penicillin	2 years (n=3) 4 years (n=1)
Gomez-Olles et al., 2010	Case report	Spain	1	Colistin	1 year
Lee et al., 2004 [111]	Case report	S. Korea	2	Cephalosporin intermediate	26 – 27 months
Menon and Das, 1977	Case report	India	1	Tetracycline	1 year
Moscato et al., 1995	Case report	Italy	1	Penicillin/ piperacillium sodium	22 months
Pala G et al., 2009	Case report	Italy	1	Cephalosporin intermediate	8 months
Sastre et al., 1999	Case report	Spain	1	Cephalosporin	9 months
Stenton et al., 1995	Case report	UK	1	Cephalosporin	1 year
Suh et al., 2002	Survey of 31 exposed with 11 symptomatic (2 of 11 confirmed OA) versus 30 controls	S. Korea	2	Cephalosporin	NA
Ye et al., 2006	Case report	S. Korea	3	Thiamphenicol	NA
Bulk laxatives					
Bardy et al., 1987	Survey of 130 workers with 39 reporting OA symptoms	Canada	5	Psyllium	NA
Goransson and Michaelson, 1979	Survey of 64 exposed workers with 27 reporting OA symptoms	Sweden	27	Psyllium	1 day to 6 months but mostly within 2 months of exposure
Marks et al., 1991	Survey of 125 exposed workers	Australia	8	Psyllium	NA
Acid blockers					
Coutts et al., 1984	Examination of 4 exposed workers with respiratory symptoms	UK	1	H2 antagonist/ Cimetidine	NA
Dally et al., 1980	Case report	UK	3	H2 antagonist/ Cimetidine	NA
Antihypertensives					
Deschamps et al., 1995	Case report	UK	1	ACE inhibitor/ Lisinopril	1 year
Harris et al., 1979	Case report	UK	1	Methyldopa	2-3 months
Enzymes					
Baur and Fruhmann, 1979	Case report and subsequent testing on 6 workers sensitized to another enzyme, papain	Germany	1 index case	Protease of pineapple/ Bromelain	10 years
			2	Papain	NA

Cartier et al., 1984	Case report	Canada	1	Pepsin	1 ½ years
Laukkanen et al., 2007	Case report	Canada	1	Lactase	1 year
Muir et al., 1997	Survey of 207 exposed workers	Canada	20	Lactase	1 ½ months
Novey et al., 1980	Survey of 23 exposed workers	US	12	Papain	12 – 15 months
Opiates					
Agius, 1989	Case report	UK	1	Morphine	About 6 years
Biagini et al., 1992	Survey of 39 exposed and 17 unexposed workers	Spain	10	Morphine, codeine, dihydrocodeine, oxycodeine, hydrocodone	1 year (n=4) NA (n=6)
Moneo et al., 1993	Survey of 28 exposed workers	Spain	6	Morphine, codeine	NA
Ulinski et al., 1996	Case report	Poland	1	Morphine	3 years

NA = Not available

Table 6: Case reports and surveys on occupational asthma.

Reference	Investigation	Location	Number of cases	Product class/name	Latency period for sensitization
Antiulcer Agents / Acid blockers					
Alomar et al., 1987	Case report	Spain	1	H_2-antagonist/ Ranitidine	~ 1 year
Conde-Salazar et al., 2007	Case report	Spain	2	Proton-pump inhibitor/ Omeprazole	NA
Guimaraens et al., 1994	Case report	Spain	3	H_2-antagonist/ Famotidine	1 ½ to 5 months
Neumark et al., 2011	Case report	Israel	1	Proton-pump inhibitor/ Pantoprazole	6 years
Romaguera et al., 1990	Case report	Spain	1	H_2-antagonist/ Ranitidine	2 weeks
Ryan et al., 2003	Survey of 8 with suspected contact dermatitis	UK	7	H_2-antagonist/ Ranitidine	< 1 year (n=3) 2 years (n=1) >2 years (n=3)
Vilaplana and Romaguera, 2001	Case report	Spain	1	Proton-pump inhibitor/ Lansoprazole	3 ½ years
Process Intermediates					
Bonamonte et al., 2002	Case report	Italy	1	2-amino-thiophenol	15 days
Deschamps et al., 1988	Case report	France	2	Diethyl-β-chloroethylamine	1 -3 hours
Goossens et al., 2006	Case report	France	1	Cinnamyl chloride	2 weeks
Jolanki et al., 1997	Case report	Finland	1	5-chloro-1-methyl-4-nitroimidazole	NA
Lerman et al., 1995	Survey of 34 potentially exposed workers	Israel	9	Ethylene oxide	2 weeks
Niklasson et al., 1990	Case report	Sweden	1	4-nitrophenyl-N-2-chloroethyl carbamate, 4-nitrophenyl-N-2-chloroethyl-N-nitrosocarbamate	2 months
Pickering et al., 1982	Case report	UK	6	4,7-dichloroquinoline	≤ 3 months (n=4) 11 months (n=1) NA (n=1)
Antibiotics					
Lopez-Lerma et al., 2009	Case report	Spain	1	Azithromycin	2 months
Malaiyandi et al., 2012	Case report	Canada	2	Tylosin	1 ½ years for 1st case 6 months for 2nd case
Milkovic-Kraus and Kanceljak-Macan, 2001	Case report	Croatia	1	Azithromycin	NA

Milkovic-Kraus and Kanceljak-Macan, 2007	Survey of 21 exposed workers	Croatia	6	Azithromycin	2-3 months to 1-3 years
Mimesh and Pratt, 2004	Case report	Canada	2	Azithromycin	NA
Non-opioid analgesics					
Kerr et al., 2008	Case report and occupational safety investigation of 8 workers with reported symptoms	UK	2 index cases and 3 more cases	NSAID/ Carprofen	< 1 day for 1st case 1 week for 2nd case NA for new cases
Kiely and Murphy, 2010	Case report	UK	1	NSAID/ Carprofen	< 1 day
Walker et al., 2005	Case report	UK	2	Analgesic/ Paracetamol	1 ½ years for 1st case NA for 2nd case
Walker et al, 2006	Case report	UK	2	NSAID/ Carprofen	3 weeks
Opioid analgesics					
Condé-Salazar et al., 1991	Case report	Spain	2	Morphine, codeine and thebaine	1 year for 1st case NA for 2nd case
Romaguera and Grimalt, 1983	Case report	Spain	5	Codeine	NA
Sasseville et al., 2011	Case report	Canada	1	Morphine	< 1 week
Waclawski and Aldridge, 1995	Case report	UK	1	Thebaine, codeine	1 ¾ years
Wootton and English, 2012	Case report	UK	3	Oxycodone	NA
Cancer drugs					
Dastychová and Semrádová, 2000	Case report	Czech Republic	1	Cisplatin	NA
Dastychová, 2003	Case report	Czech Republic	1	Methotrexate	2 months
Jungewelter and Aalto-Korte, 2008	Case report	Finland	1	Anti-androgen drug/ Flutamide intermediate	1 hour
Lahti et al., 1990	Case report	Finland	1	Methotrexate	1 day
Antihypertensives					
Ekenvall and Forsbeck, 1978	An investigation on 32 workers with suspected dermatitis out of 300 surveyed workers	Sweden	14	Beta blocker/alprenolol	< 1 year (n=13) > 5 years (n=1)
Valsecchi et al., 1994	Case report	Italy	1	Beta blocker/ Propranolol	10 months
Statins					
Field et al., 2007	Case report	Ireland	1	Simvastatin	NA
Field et al., 2008	Case report	Ireland	1	Simvastatin	NA
			2	Atorvastation	NA
Peramiquel et al., 2005	Case report	Spain	2	Simvastatin	2 days for one case NA for the 2nd case

NA = Not available

Table 7: Case reports and surveys on contact dermatitis (CD).

latency periods from exposure to the onset of OA ranged from one to six years in the investigations where this information was reported [47,48,50].

Bulk laxatives: Three investigations have documented OA in workers exposed to psyllium (isphagula) [51-53]. Goransson and Michaelson surveyed 64 workers and found that 27 (42.2%) reported OA symptoms that occurred after an exposure that lasted a few hours to six months; however, these workers developed symptoms within two months of exposure [52]. Bardy et al. surveyed 130 workers at a pharmaceutical plant that manufactured psyllium. 39 workers reported symptoms that were suggestive of occupational asthma; however, only 14.3% of 35 (n = 5) workers evaluated had a confirmed OA diagnosis when objective measures were for the diagnosis [53]. Marks et al. examined 125 psyllium-exposed workers and compared their respiratory symptoms and sensitization to psyllium to a reference population of 738 randomly selected adults from the local community. Exposed workers had a higher prevalence of respiratory and skin symptoms than the reference population (52.0% vs. 43.3%). Workers who were sensitized to psyllium were more likely to develop symptoms if they were current smokers. Although 6.8% of workers had OA, only 3.2% had an OA diagnosis that was based on objective measures [51].

Acid blockers: Two investigations documented a total of four OA cases associated with exposure to the acid blocker, cimetidine [54,55], but neither of these investigations documented the latency period.

Antihypertensives: OA was documented in two case reports related to exposure to antihypertensives. The latency period for the development of symptoms from exposure to the angiotensin-converting enzyme (ACE) inhibitor, lisinopril, was one year [56] while the latency period for the central α-agonist, methyldopa, was 2-3 months [57].

Contact dermatitis: Contact dermatitis (CD) is the most common occupational skin disease, and it accounts for 90% to 95% of all cases involving the skin [58]. Allergic skin reactions, primarily, contact dermatitis (CD), have also been documented in workers involved in the manufacture of various pharmaceutical products especially acid blockers [59-65] and product intermediates [66-70]. It should be noted that confirmatory medical testing, typically patch testing, was used to confirm these independent diagnoses of CD from the skin exposure to the API or process intermediates.

Acid blockers: Both classes of acid blockers have been linked to the incidence of CD. There are four reports of H_2 antagonist-related CD in 12 workers, and eight of twelve CD cases developed symptoms within one year [59,61,63,71]. The three reports regarding proton-pump inhibitors documented a total of four cases diagnosed with CD [60,62,64]. Symptoms developed after 3½ years of exposure in one study [64] while symptoms developed after six years in the second one [62]. However, the latency period was not documented in the third study of proton-pump inhibitor-related CD [60].

Product intermediates: Product intermediates have demonstrated to cause CD in 21 cases in seven reports [66-70,72]. Nineteen of the 21 cases developed symptoms in less than one year [66,67,70]. The two remaining cases were missing information on latency period [68,70].

Antibiotics: Five reports have documented the incidence of CD among workers exposed to antibiotics during production [73-77]. Four of these reports documented azithromycin-related CD in a total of 12 workers, and this allergic response occurred within three years of exposure [73,75-77]. The fifth investigation reported tylosin-related CD in two cases that occurred within 6-18 months of exposure [74].

Non-opioid analgesics: There are four reports that document CD in individuals exposed to non-opioid analgesics like carprofen [78-80] and paracetamol (also known as acetaminophen) [81]. In these reports, the workers profiled developed symptoms within 1½ years of exposure. Three reports on eight CD cases implicated the nonsteroidal anti-inflammatory drug, carprofen, with symptoms within three weeks of exposure among five of these eight cases [78-81]. In a fourth investigation, Walker et al. reported the incidence of CD in two workers who had been exposed to paracetamol. One worker developed symptoms after 1½ years of exposure to paracetamol, but the latency period in the second case of CD was not reported [81].

Opioid analgesics: A variety of opiates have been implicated in the occurrence of twelve CD cases documented in five case reports [82-86]. CD was evident within two years of exposure in four reports. Codeine exposure was reported in three reports [82], one report documented oxycodone-related CD, while two reports documented morphine-related CD [82, 84] or thebaine [82,85].

Anti-cancer drugs: Four case reports each documented one case of CD resulting from exposure to anticancer drugs or process intermediates [87-90]. Three of the four cases developed symptoms within two months after exposure [88-90]. The fourth case report did not provide information on latency [87].

Antihypertensives: The incidence of CD in 15 cases was reported among workers exposed to beta-blockers in two investigations [91,92]. There were 32 workers with suspected AC, but only 14 of these cases had confirmed CD. Thirteen of these cases developed symptoms within one year and the remaining case developed symptoms after more than five years [91]. In another case report of antihypertensive-related CD, a worker developed symptoms after 10 months of exposure to propranolol [92].

Statins: Three case reports documented incidence of six cases of CD related to exposures to the statins, simvastatin, and atorvastatin [93-95]. The latency period for one case was two days [94], but this information was unavailable for the remaining four cases [93-95].

Other adverse health effects: Although most case reports have documented allergic disease in pharmaceutical workers, there is documentation of other adverse health effects among these workers. These ill health effects have included structural changes in the eyes [96], accelerated clotting function associated with manufacturing estrogen-progestin combinations for oral contraceptive pills [97], hypoglycemia due to the exposure to anti-diabetic medicines like sulfonylureas [98] and diuretic and hypotensive effects associated with manufacturing antihypertensive medication [99], and acquisition of antibiotic-resistant bacteria [100].

Discussion

We sought to conduct a qualitative assessment of the extant literature on the occupational health of pharmaceutical production workers. We found that relatively few studies have been conducted to examine the occupational health of these workers. Many of the investigations had been prompted by suspected disease clusters [4,5,10], or reports of adverse health effects among some workers [20,25]. A variety of study designs have been used to characterize health outcomes in this population, and each design has its merits and limitations.

Mortality studies

Five of seven mortality studies in this review showed that pharmaceutical production workers had a better overall mortality experience than their reference population [4-6,10,11]. Similarly, these studies showed that pharmaceutical workers had similar or lower all-cancer mortality than the general population. These findings suggest a healthy worker effect, a common confounder in occupational studies [101]. This effect may be partly explained by differences between the cohort and referent populations that may include better health status [102], health care benefits[103], and socioeconomic status among the cohorts than the reference populations [101]. One mortality study minimized this confounding effect by using internal controls [9]. The two remaining mortality studies found that pharmaceutical workers had a higher than expected cancer mortality risk [9,12]. The study by Baker et al. reported that female workers had excess overall cancer mortality while the study by Thomas and Decoufle reported an excess for cancer mortality in both sexes.

Cause-specific mortality experience of the cohorts tended to vary across studies. Mortality excesses that were evident in two or more studies included colon cancer [9,11], breast cancer [9,12], respiratory system cancers [5,6,10], and lymphohematopoietic cancers [5,6]. Mortality excesses evident in some studies were not observed in other studies; Thomas and Decoufle reported an elevated mortality due to suicide or cervical cancer [12], while Edling et al. found an elevated risk of urothelial cancer [10].

Of all seven mortality studies reviewed, only one included a nested case-control study to evaluate the association between specific exposures and health outcomes, independent of confounding factors [6]. As in the earlier study by Marsh et al. [5], the nested case-control study by Youk et al. [6] did not find a relationship between any specific occupational factor and the risk of respiratory system and lymphohematopoietic cancers. There were a small number of total cases due to the rarity of these cancers. Thus, both studies could not examine the relationship of occupational factors with these cancers.

While mortality studies are useful for the characterization of the mortality experience of production workers, three studies did not have the occupational data necessary to examine the relationship work history and occupational exposure with mortality [9,11,12]. The three studies with data on occupational exposure did not find an association of occupation and mortality [4-6]. Similarly, Edling et al. failed to find this association [10].

Cancer morbidity

The overall cancer incidence among production workers was similar to the incidence in the general population in two studies [10,14]. Production workers were found to have elevated incidences of breast cancer [10,14], leukemia [10,13], and urothelial cancer [10]. The excess cases of breast cancer and leukemia among production workers [13] was consistent with the excess risk of cancer evident in the mortality studies by Thomas and Decoufle [12] and Edling et al. [10]. However, the studies reporting an elevated risk for breast cancer did not address the confounding associated with reproductive history (e.g., delayed childbirth, use of oral contraceptives, or nulliparity) that increase a woman's risk of breast cancer.

All three cancer morbidity studies failed to show any consistent relationship between cancer incidence and any specific occupational risk factor [10,13,14]. In other studies, the relationship between occupational factors and cancer risk could not be determined because occupation history was unavailable [13] or because information about potential confounding factors including medical history was not ascertained [10]. The adjustment for these non-occupational factors is important especially given that the long latency period and multicausal nature of carcinogenesis.

Liver disease

The studies on liver disease yielded consistent findings. The cross-sectional study by Tomei et al. [15] suggested that occupational exposure may increase the risk of liver toxicity among pharmaceutical production workers exposed to xenobiotics. The hospital-based case-control study by Heinemann et al. demonstrated a statistically insignificant increase in liver cancer (OR = 2.44) in female pharmaceutical workers was reported [16].

The study by Tomei et al. had three major limitations. First, the source of the study controls was not discussed. Second, this study did not specify the cutoff points used to classify the liver function test results. Third, these investigators did not quantify the strength of independent association between liver toxicity and occupational exposure despite an extensive investigation to identify potential confounding factors. The study by Heinemann et al. did not validate the history of exposure and employment, and it is unknown if any of the eight female pharmaceutical industry workers worked in production. It is possible that there may have been differential recall of lifetime exposure and work history among cases and controls. In addition, this study had an insufficient number of cases and controls for the examination of liver disease by occupation group.

Reproductive function

Occupational studies on reproductive function focused on the effects of organic solvents on female fertility and on the estrogenic effects on male sexual function.

Organic solvent exposure: The findings by Taskinen et al. are corroborated by recent meta-analysis by McMartin et al. that found that exposure to solvents was not significantly associated with the risk of spontaneous abortion [104]. Exposure to organic solvents during pregnancy was associated with a 64% higher risk of major malformations than non-exposure. However, this meta-analysis was not confined to studies on occupational exposures in the pharmaceutical industry. The study by Taskinen et al. lacked information on the smoking history of 25% of the women and on previous pregnancy history of 41% of women, and spontaneous abortion was not defined in this study. Although the study was conducted over a seven-year period during which occupational exposures decreased, this study did not account for temporal changes in solvent exposure.

Estrogen exposure: Estrogen exposure was found to be associated with a history of gynecomastia [20,24] or a disruption in reproductive function in exposed workers [22,24,105]. Other studies found that estrogen exposure was associated with abnormal levels of reproductive hormone levels in workers [21,23] or changes in hematological, hepatic or metabolic factors [23]. None of these studies led to published longitudinal studies to report on the long-term morbidity (e.g., increased risk for hormonally-related cancer, liver disease, blood clots, infertility, or birth defects) or mortality experience of these exposed groups of workers.

The study by Harrington et al. lacked information on contraceptive history for study controls. Shmunes and Burton provided limited information on employment status by exposure, and the relationship of the environmental measurements to the urinary DES level measurements was unclear [20]. Rao et al. examined the adverse health effects experienced by men and women exposed to sex steroids and nonsteroidal APIs, and they reported hormone levels by exposure levels. Both Willems and Shamy et al. examined the relationship of the observed abnormal hormone levels to exposed workers, but they did not examine the incidence of hyperestrogenic effects associated with this exposure. Shamy et al. also compared the biochemical profile of exposed workers and controls; however, they did not evaluate prior reproductive function, or chronic conditions such as liver disease, cardiovascular disease, diabetes, and renal disease. This latter did not account for potential confounding related to reproductive function and health status.

Adrenal dysfunction

A case report and a subsequent survey by Newton et al. documented an association between exposure to glucocorticoids and a decline in cortisol levels in exposed workers [25,26]. In contrast, Phillips failed to find an association between glucocorticoids and suppressed function but found an increased incidence of allergic skin reactions to the glucocorticoids [27]. Newton reported that adrenal function disruption was associated with dosage rather than the duration of exposure [25]. These three studies had limited information on the exposure levels associated with adrenal dysfunction and skin reactions. The major weakness of these studies was the failure to publish longitudinal evaluations of the morbidity (e.g., cardiovascular, endocrine, or liver function issues), and mortality experience of these workers. In particular, it would have been valuable to understand whether the potential for suppression of the immune system that may have rendered exposed employees more susceptible to infection and cancer actually occurred, and what the associated chemical exposure profiles were for these workers.

Allergic diseases

The preponderance of investigations on the occupational effects of pharmaceutical manufacturing on the health of workers are case reports that document allergic sensitization involving the skin or respiratory

system. In a few of these case reports, cross-sectional surveys of other exposed workers were initiated following the symptoms found in index cases [55,106]. In survey investigations that were conducted, comparisons were made between exposed and unexposed workers [53,107] or to the general population [51].

Case reports often lack the scientific rigor necessary for the conduct of epidemiologic studies. These reports, bolstered by independent clinical tests, can confirm the occurrence of dermal sensitization to various occupational exposures to APIs and process intermediates. Taken together, case reports and clinical testing can used to identify occupational hazards, detect emerging diseases, generate research hypotheses, and they can be used in pharmacovigilance. Despite the merits of case reports, few occupational health studies have been conducted based the findings of these reports.

Conclusion

The lack of detailed exposure information and the paucity of longitudinal studies of production workers is a major limitation in the occupational health research conducted in the pharmaceutical industry. More research is needed to elucidate the relationship between workplace exposures and health outcomes. Currently, there are few consensuses or regulatory standards for occupational exposure limits in the pharmaceutical industry. Consequently, industrial hygiene and medical history databases need to be implemented and supplemented with comprehensive epidemiological studies. With these changes, future investigations would be able to determine the short-term and long-term occupational health effects related to the manufacture of pharmaceutical products. This is an opportune time to implement these changes especially as production operations are continually transferred abroad, especially to Asia [108]. Given the overarching goal of reducing exposure of production workers to hazardous pharmaceutical products, we recommend that future occupational studies address the methodological challenges discussed herein.

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Conflict of Interest Statement

IG is Instructor of Pharmacy and Therapeutics at the University of Pittsburgh, School of Pharmacy. She has no competing interests to declare.

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Author Contributions Statement

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