

## IN-DEPTH REVIEW

# Health effects of exposure to active pharmaceutical ingredients (APIs)

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<b>Background</b>	Workers involved in the manufacture of pharmaceutical products are exposed in the course of their work to the active pharmaceutical ingredient (API) in the products. Such APIs are designed to produce biological change in the human body, which is an unacceptable outcome in the pharmaceutical worker.
<b>Aim</b>	To review the evidence for the presence of the health effects of APIs in the pharmaceutical industry.
<b>Method</b>	The study employed a literature review based on a systematic search of the MEDLINE database.
<b>Results</b>	Studies have shown that such biological effects can be produced, particularly in personnel working with potent compounds such as steroids, compounds with capacity to cause cumulative damage such as cytotoxic anti-cancer drugs and antibiotics, unless careful risk assessment and appropriate control measures are implemented.
<b>Conclusion</b>	There is limited epidemiological evidence for increased mortality and morbidity in this population, but adverse effects on health from exposure to potent agents, such as corticosteroids, sex hormones and antibiotics, can occur. The protection of workers from the potential harmful effects of APIs poses a significant challenge for the pharmaceutical industry.
<b>Key words</b>	Active pharmaceutical ingredient; acute pharmacological effects; bronchoconstriction; epidemiology; health effects; morbidity; mortality; occupational disease; respiratory sensitization; skin sensitization; steroids.
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## Introduction

Workers involved in the manufacture of drug substances can be exposed to active pharmaceutical ingredients (APIs) designed with the express intention of an interaction with the human system and modification of its functioning. Whilst such modification is generally desirable in patients, any modification in function,

whether positive or negative, is an unacceptable outcome in the pharmaceutical industry worker.

In addition, developments in research for new compounds and research techniques are creating new hazards. The process of delivering new medicines from research idea to prescribed medicine takes much longer than many expect and during the early part of this discovery and development process there is the potential for small teams of scientists to be exposed to uncharacterized and untested therapeutic agents. Meanwhile, the technological basis of the industry is rapidly changing. New methods of identifying biologically active compounds by high-throughput screening techniques using cloned receptors are producing compounds with ever-increasing potency, sometimes in

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the microgram range. In addition, new ranges of therapeutic agent are being developed based on a rapidly increasing understanding of the functioning of the human cell and the relationship between the activity of genes and the functions of the proteins they manufacture (genomics and proteomics). Using these techniques, biological compounds such as antigens can be produced which modify cell function in a fundamentally different way to traditional chemical therapeutic agents. Our knowledge of the hazards linked to these techniques is still in its infancy and understanding of these hazards is one of the major challenges for the future.

As the drug development cycle progresses, pharmaceutical agents are subject to comprehensive regulatory testing, both for efficacy and safety, and detailed pre-clinical and clinical toxicology information is generated, upon which worker occupational exposure limits can be based. However, despite comprehensive risk management systems, studies have shown that worker health effects have been experienced in the industry, particularly in personnel working with potent compounds such as steroids, or compounds with the capacity to cause cumulative damage, such as cytotoxic anti-cancer drugs.

## Method

To carry out this review, a systematic search of the MEDLINE database was undertaken (1966–November 2002) using subject heading and key word searches for ‘pharmaceutical industry’ and ‘pharmaceutical manufacture’, together with terms for ‘occupational exposure’, ‘worker health’, ‘overexposure’ and ‘hazardous substance’. All of the abstracts were reviewed and major articles retrieved and examined. In addition, bibliographies of existing reviews were studied and further references followed up. In particular, the reviews by Teichmann *et al.* [1] and Huyart [2] were of value in this respect.

## Acute pharmacological effects

Most harmful effects resulting from exposure to pharmaceutical agents are the result of acute pharmacological effects, although reports in the literature are relatively rare. It is possible that this reflects conservative occupational exposure limit setting practices, together with short-term exposure patterns and effective exposure controls. It is also possible that many mild cases are only reported internally and are not published. Among those which have been published is the case presented by Albert *et al.* [3], in which an operator working on the manufacture of glibenclamide was admitted to hospital in hypoglycaemic coma and the report of a study by Baxter *et al.* [4], in which operators were found to have absorbed significant levels of barbiturates.

## Chronic effects from potent compounds

The problems of highly potent compounds are highlighted by the case presented by Jibani and Hodges [5], in which an operator suffered severe effects from the excessive absorption of vitamin D3. This case is unusual, however, as the most common problems reported in the literature have been linked to exposure to two specific types of potent compound: steroid hormones and cytotoxic anti-cancer drugs.

### Steroid hormones

#### *Oestrogens and progestagens*

The first report of adverse effects in workers related to oestrogens dates back to 1942, when Scarff and Smith [6] noted the development of gynaecomastia and loss of libido in men working with diethylstilboestrol.

A series of reports throughout the 1970s and 1980s highlighted the problems of steroids, including those of Suciu *et al.* [7], showing an increase in psychological effects, testicular discomfort and loss of libido in workers manufacturing acetoprogesterone.

An important study was conducted by Harrington *et al.* [8] looking at workers exposed to synthetic oestrogens. Of the 25 men studied, five were found to have effects linked to steroid exposure, including gynaecomastia, loss of libido and galactorrhoea. Of the 30 women, 12 were found to have menstrual breakthrough bleeding, a rate four times more frequent than that in the control population. This study is interesting, as an attempt was made to link clinical effects to exposure levels and biological markers such as the plasma drug levels. The interpretation of the plasma drug levels proved difficult, as the relationship to exposure was not clear. To understand the true level of exposure, a series of samples is required over a defined period of time to determine the area under the exposure versus plasma concentration curve. It was, however, noted that the levels were higher in the workers with the higher exposure.

Further studies by Shmunis and David [9] investigating workers exposed to diethylstilboestrol and Mills *et al.* [10] confirmed the prevalence of problems at very low levels of exposure.

Taskinen *et al.* [11] conducted a register-based, case-control study on the pregnancy outcome of female workers in eight Finnish pharmaceutical factories to determine whether they had a higher risk of spontaneous abortion than the general population or matched controls. In a logistic regression model (which included oestrogen exposure, solvent exposure frequency of usage and heavy lifting), the odds ratio (OR) was increased for oestrogens (OR = 4.2,  $P = 0.05$ ), as well as for continuous heavy lifting (OR = 5.7,  $P = 0.02$ ). However, it is difficult

to identify the contribution of the different exposure components to this finding.

In a more recent study, Shamy *et al.* [12] investigated workers exposed to ethinyloestradiol, levonorgestrol and progesterone in the manufacture of oral contraceptives. The study looked at 18 men and 34 women. The women were principally performing blister packaging tasks and were selected as being post-menopausal for at least 2 years. The study found that oestrogen levels were significantly increased in both sexes and there was a decrease in testosterone in the male workers. There was no difference in progesterone or gonadotrophins between the exposed and control groups. The authors concluded that liver dysfunction might have been responsible for the changes in levels.

### Corticosteroids

Newton *et al.* [13] found a diminution in corticotrophins and grossly abnormal synacthen test results in two out of 12 workers involved in the manufacture of betamethasone (no exposure data were provided). A 1987 case report by Pezzarossa *et al.* [14] describes a pharmaceutical worker involved in micronization of steroids, who was also found to have symptomatic and biochemical adrenal suppression. Total dust measurements in the work area showed values of 3.1 and 12.8 mg/m<sup>3</sup> (the proportion of corticosteroid in the dust being 80% w/w). Six months after removal from exposure, hormonal and metabolic features of adrenal suppression had largely subsided. In 1988, Moroni *et al.* [15] studied a factory in which corticosteroids were manufactured. Adverse effects found included local effects on the skin such as acne and erythema and systemic effects, including hypertension and effects suggestive of Cushing's syndrome. The skin manifestations improved during vacation periods and worsened during more intense work periods. However, they were unable to demonstrate a clear relationship between the clinical manifestations and the levels of urinary 17-OH corticosteroids or plasma cortisol. It is likely that these levels changed very rapidly in response to the level of corticosteroid absorbed, making them difficult to use as a reliable biological marker.

The evidence suggests that occupational steroid-related skin conditions may be induced by both systemic or local exposure and that in most cases the effects are reversible on cessation of exposure.

### Cytotoxic anti-cancer drugs

The theoretical health risk from exposure to these drugs is very high. Although the therapeutic dose may be relatively high, the therapeutic index is usually low. Also, unlike other drugs, therapeutic use involves pushing doses to the limits of toxicity. These drugs can exert biological effects even at very low levels of absorption.

Also, as dosages are high, the quantities handled by workers—and therefore the level of potential exposure—can be significant, which is unlike the situation with other potent compounds.

The main studies in the pharmaceutical industry have been by Sessink *et al.* [16], who in 1993 studied exposure to methotrexate in a secondary manufacturing site. Atmospheric levels as high as 182 µg/m<sup>3</sup> were found in the area in which the powders were dispensed. Urinary excretion of methotrexate was used as a method of determining absorption and an average level of 13.4 µg in a 24 h period was found. The workers in the area wore a high level of respiratory protection and the authors concluded that skin absorption was a major factor. In 1994, Sessink [17] studied exposure to 5-fluorouracil by the measurement of a metabolite. Again, significant exposure in the dispensing area was found and significant contamination of the work surfaces within the work area was detected, which would provide opportunity for skin uptake.

## Respiratory sensitization and bronchoconstriction

The development of adverse pharmacological effects is not the only problem associated with exposure to pharmaceuticals. Respiratory sensitization has been noted in relation to exposure to several compounds. Two groups of compounds have been particularly implicated: penicillin and cephalosporin antibiotics [18,19] and enzymes [20–23].

Other chemical therapeutic agents noted to cause such problems include cimetidine [24], lisinopril [25],  $\alpha$ -methyldopa [26] and salbutamol [27]. It is not always clear in these cases whether the effect was sensitization or secondary to a direct pharmacological effect caused by an action of the inhaled dust on the respiratory tract. A particular problem is posed by the association of bronchoconstriction with exposure to opiates. This has been reported by Agius [28], Biagini *et al.* [29] and Gorski and Ulinski [30]. Biagini *et al.* [31] were able to demonstrate the presence of antibodies to opiates. However, opiates are also known to have a histamine releasing effect and it is possible that this forms the basis for their broncho- constrictive properties.

## Skin sensitization

Contact reactions resulting from skin exposure have been reported in connection with pharmaceutical manufacture. The underlying causes and steps for worker protection are unchanged from those regarding any potential skin sensitizer or irritant.

Skin sensitization has been noted in relation to the exposure to several compounds. Examples include

Table 1. Case control studies

Study	Cases studied	Finding
Notani <i>et al.</i> [40]	Cancers of the lung and bladder	Statistically significant elevated risk was observed for chemical pharmaceutical plant workers (OR = 4.48; 95% CI = 1.2–16.5). However, this included workers in primary fine organic chemical manufacturing sites, who are likely to be exposed to aromatic amines and other compounds known to carry a risk of bladder cancer
Heinemann <i>et al.</i> [41]	Hepatocellular cancer (HCC) in women	Women working in the pharmaceutical industry were shown to have an increased OR of 2.44 (0.77–7.73), but owing to the small number of cases (three), this was not statistically significant

Table 2. Cohort studies

Study	Population studied	Findings
Baker <i>et al.</i> [42]	Mortality in British pharmaceutical industry workers	Statistically significant increase for breast cancer risk with an OR of 2.90 (1.67–5.05) and for all cancers with an OR of 1.65 (1.07–2.54)
Harrington and Goldblatt [43]	Mortality in British pharmaceutical industry workers	There was no evidence, on the basis of this study, to suggest any excess mortality risk from employment in the pharmaceutical industry
Edling <i>et al.</i> [44]	Mortality and cancer incidence in laboratory and production workers at a pharmaceutical company	A significant increase in the risk for urothelial tumours was found among pharmaceutical workers, the standard incidence ratio (SIR) being 2.3 (0.84–5.0) with 10 year latency and for acute leukaemia 4.5 (1.2–12)
Hansen <i>et al.</i> [45]	Cancer morbidity in workers at a Danish plant, where enzymes, insulin, antibiotics and sex hormones were produced in substantial quantities	A significantly elevated SIR for women 1.2 (1.03–1.30). Excess risk was particularly seen for breast cancer [SIR = 1.5 (1.2–1.8)], especially in a subgroup who had started work at the factory aged 30–39 and had continued to work for 1–9 years (SIR = 2.8). The SIR was near unity for men ( <i>n</i> = 5335); however, three men were found with breast cancer, versus 0.4 expected. Lifestyle components explained only about one-quarter of the excess female breast cancers

contact sensitivity, reported to the H<sub>2</sub> receptor antagonist ranitidine in a manufacturing operation [32]. The importance of enclosure and employee education were noted as potential measures for reduction of future cases. Unprotected exposure to an intermediate used in the manufacture of cimetidine has also been implicated as a cause of an acute erythema multiforme-like reaction [33]. There have been case reports of allergic reactions to proton pump inhibitors [34] and allergic contact dermatitis has also been infrequently reported in the handling of cytotoxic medicines, including mechlorethamine [35], nitrogen mustard [36], mitomycin C [37] and carmustine [38] and, more recently, in a quality-assurance worker handling melphalan and chlorambucil [39].

Epidemiological studies

Very few epidemiological studies of workers in the pharmaceutical industry have been carried out (Tables 1 and 2). From these, it is difficult to draw any firm conclusions, although the majority do not indicate firm evidence for increased mortality or morbidity.

These studies indicate that, apart from a group exposed

to sex hormones before modern methods of exposure control had become widely established, no significant exposure-related excess morbidity or mortality has been identified in workers in the pharmaceutical industry

Conclusion

The protection of workers from the potential harmful effects of APIs poses a significant challenge for the pharmaceutical industry, due to the inherent biological activity of the chemicals manufactured. Although there is limited epidemiological evidence for increased mortality and morbidity in this population, adverse effects on health from exposure to potent agents such as corticosteroids, sex hormones and antibiotics can occur unless careful risk assessment and appropriate control measures are implemented. The latter are discussed in an accompanying review by Binks [46] on occupational toxicology and the control of exposure to pharmaceutical agents at work.

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