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OCCUPATIONAL EXPOSURE LIMITS FOR THERAPEUTIC SUBSTANCES*

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Abstract—Few therapeutic substances have occupational exposure limits (OELs) set by regulatory bodies and reliance is often placed on in-house OELs derived from a formula based on the therapeutic dose. This mode of derivation relies on assumptions about pharmacokinetics, pharmacodynamics and risk acceptability which might not be soundly based for occupational health purposes.

Pharmacodynamic evidence shows that occupational exposure to airborne therapeutic substances can be associated with a much higher risk of an adverse health effect especially on the lungs or skin than by their therapeutic administration. Pharmacokinetic studies indicate that for certain therapeutic substances occupational exposure by inhalation results in a more rapid and complete systemic absorption than a similar dose administered (usually orally) for therapeutic purposes.

These and other considerations are used to develop a systematic strategy for deriving OELs for therapeutic substances. The first stage of this consists of a qualitative assessment and ranking of likely occupational health effects. This is based on pharmacological studies, analogy and specific workplace studies. Subsequently assessment of the relevant pharmacological data together with environmental monitoring and exposure-linked health surveillance provides the quantitative data for the setting of appropriate OELs.

> 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.
> B. RAMAZZINI, 1713

INTRODUCTION

RAMAZZINI'S remarks, quoted above, show that the existence of health hazards from the manufacture and handling of therapeutic substances has been suspected for nearly three centuries. More recent reviews of the risks include those by WATROUS (1947), HARRINGTON (1981) and TEICHMAN *et al.* (1988). A therapeutic substance may be defined as a substance administered with the intention of treating or preventing disease. However for the purposes of this paper precursors of these substances, which may share their biological properties, or substances developed with a therapeutic intent but not marketed may also be included.

In Britain, responsibility for reducing, so far as is reasonably practicable, the work-related health risks in all industries including the pharmaceutical industry was consolidated within the Health and Safety at Work, etc., Act, 1974. The 1989 edition of Guidance Note EH40 (HEALTH AND SAFETY EXECUTIVE, 1989a) quotes occupational exposure limits for only five therapeutic substances in current use. The Control of Substances Hazardous to Health (COSHH) Regulations (HEALTH AND SAFETY

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COMMISSION, 1988) apply to therapeutic substances in an occupational context although they are not applicable when the substances are administered in the course of medical treatment (Regulation 5). The Approved Code of Practice (ACOP) of the COSHH Regulations envisages the setting of occupational exposure limits (OELs) by the employer where there is sufficient information for him to do so (paragraph 29). Pharmaceutical companies have recently become increasingly aware of the need to derive their own 'in-house' OELs (SARGENT and KIRK, 1988; MCHATTIE *et al.*, 1988).

The ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY (ABPI) (1985) has recognized that an integral part of the health risk reduction strategy must include the setting of OELs, and has stated that there is no simple formula or checklist for their derivation. It has thus considered an alternative approach to the setting of OELs by the demonstration that at the level achieved by the manufacturing procedures used (working limit) no adverse effects are observable. This however is not a satisfactory alternative to an OEL, as in practice many working limits may be set without a complete systematic assessment of the potential health effects and therefore adverse effects might not be observed because they are not specifically sought. Moreover the environmental monitoring strategy and time-weighting assumptions in the setting of working limits are often inadequately defined.

A considerable body of health-related information is generated during the development of drugs and a proportion of it can be used for the derivation of OELs, although additional information is usually needed for this purpose. One end stage of the information collected for therapeutic purposes, the therapeutic dose, is in itself of no relevance to occupational health practice. Its use as a starting point for the setting of OELs is to be discouraged for several reasons:

(i) a therapeutic dose, by definition, manifestly produces an appreciable effect on the human body, whereas OELs are intended to avoid an adverse effect on health;

(ii) it is not possible to assume a direct extrapolation from the kinetics of a dose administered therapeutically—possibly orally—to an exposure experienced occupationally usually by inhalation;

(iii) derivation of an OEL from the therapeutic dose would imply the assumption that health effects are always similar, whatever the route by which the therapeutic substance is presented to the body;

(iv) OEL derivation based only on therapeutic properties does not take into account other properties such as carcinogenicity or allergic sensitization; and

(v) for the therapeutic dose to be used as a basis for an OEL it must be scaled down by a 'safety' factor which is perhaps better called an 'uncertainty' factor as it must often be established in a completely arbitrary manner.

A SYSTEMATIC STRATEGY

Therapeutic substances are no different from other substances hazardous to health in that accepted principles of occupational health practice must be applied to their study, so as to obtain the information from which OELs are derived. Moreover since the COSHH regulations incorporate many of these principles, reference will be made to them and to their approved code of practice (ACOP). In addition there is a large body of information and expertise that is specific to therapeutic substances and which should be tapped. This relates to pharmacokinetics (how the body handles the drug) and

pharmacodynamics (what the drug does to the body) (FEELY and BRODIE, 1988; GOODMAN GILMAN, 1985). A systematic approach is presented below.

Qualitative assessment of health effects

Recognition of the likely occupational health effects of therapeutic substances is necessary before these effects can be measured and the knowledge applied to OEL derivation. The effects need to be ranked so that the ones that are most relevant to short-term or long-term occupational exposure are identified. If this is not done adequately at the outset considerable effort might be expended in deriving limits designed to prevent a health effect that does not arise occupationally while adverse effects peculiar to occupational exposure might remain uncontrolled. Moreover, the nature of the adverse effect(s) on health will influence the choice of further health surveillance and environmental monitoring techniques. Paragraph 3 of the COSHH ACOP implies the use of these means to identify hazardous properties of substances, and these can be adapted for therapeutic substances as follows.

(1) *Therapeutically desired health effects*

Since these constitute the prime purpose of the therapeutic substance, liaison with pharmacologists and other scientists will determine what they are on the basis of animal and human studies. Those effects which directly and acutely modulate normal human functions such as by reduction of pulse rate or blood pressure or alteration of consciousness are likely to be occupationally relevant. Effects of therapeutic substances intended to replace normal hormones or suppress their production can have very important chronic occupational implications. On the other hand, effects such as analgesia (the suppression of pain) or the destruction of pathogenic organisms not normally present in man are likely to be occupationally irrelevant in themselves.

(2) *Therapeutically undesirable effects*

No therapeutic substance produces a single effect, and many therapeutic 'side effects' need to be ranked more highly in their occupational importance than the therapeutic intended effect. Thus, for example, the sedative effect of certain analgesics, anticonvulsants, antihistamines, antidepressants or anxiolytics may be much more relevant occupationally than their primary action. Cytotoxic agents used to treat cancer may be irritant or toxic or potentially carcinogenic or teratogenic in themselves. They present a particular problem in OEL setting since the relationships between low level exposure and long-term health risks are very difficult to quantify. Such potentially serious hazards argue for extreme caution in the long-term exposure of workers, with correspondingly stringent exposure limits.

(3) *Evidence by analogy*

Pre-marketing therapeutic experience can be a relatively poor predictor of adverse occupational effects on the organs of first contact (skin, eyes, nose and lung) especially if they are specific to humans and therefore not revealed by animal studies. However analogy with other human experience may help. Thus for example occupational asthma from the bulk laxative Ispaghula was not predictable from its therapeutic use but its plant of orgin is botanically closely related to plantain—a well known cause of

asthma. The pharmaceutical industry often employs structure activity relationships in attempting to predict desired effects of therapeutic substances and similar analyses may be used to predict side effects. Even in the absence of a formal computerized application of these techniques to occupational exposure to these substances, certain lessons can be learnt. The bicyclic beta lactam rings of various antibiotics are known to cause occupational asthma (DAVIES *et al.*, 1974; COUTTS *et al.*, 1981) and it is reasonable to suspect that their derivatives or analogues may have similar risks. Piperazine, another therapeutic substance which can cause asthma (PEPYS *et al.*, 1972) shares chemical similarities with other non-therapeutic chemicals causing asthma, such as ethylene diamine, azodicarbonamide, *p*-phenylene diamine and toluene diisocyanate since they are all small molecules having two nucleophilic nitrogen atoms.

(4) *Health surveillance*

Health surveillance, whether or not based on the above three indications of possible occupational health effects, may identify work-related adverse effects. Some of these would not have been easily predictable otherwise (AGIUS *et al.*, 1986). For the purposes of the health surveillance of a working population exposed to a therapeutic substance one should suspect that symptoms involving the organs of first contact (eyes, skin, nose and lungs) may be occupational in origin even if different from the therapeutic experience. This suspicion may need to be confirmed or refuted by an appropriate survey (VENABLES, 1989). Uncritical assumptions that adverse effects on health are idiosyncratic or occurring rarely and only in 'susceptible' individuals should therefore be avoided.

Quantitative assessments of health effects and their relationships to exposure

The aim of this stage of the strategy is to provide quantitative information relevant to the control of exposure to a level at which nearly all the population could be exposed, day after day, without adverse effects on health (COSHH ACOP 29).

(1) *Pharmacological data*

Data from laboratory animal studies and clinical trials could be used to help derive OELs (as shown by SARGENT and KIRK, 1988) provided the limitations of such techniques are recognized (ECETOC, 1984). Important differences between the pharmacokinetics of occupational exposure and the therapeutic experience need to be taken into account. Thus inhaled respirable dust consisting of a soluble therapeutic substance such as codeine will tend to be rapidly and completely absorbed into the systemic circulation. Therefore in terms of its bioavailability occupational exposure will have much more in common with intravenous administration, than with oral administration when absorption is slow, partial and subsequently subject to metabolism in the liver (DOLLERY *et al.*, 1971; PEPELKO and WITHEY, 1985).

Differences in the pharmacodynamics of occupational exposure may further limit the value of any approach derived from pharmacological data of the therapeutic relevance only. Thus, for example, SARGENT and KIRK (1988) appropriately do not consider analgesia as the relevant adverse health effect related to occupational opiate (morphine and codeine) exposure but seek to establish a limit to prevent sedation. However within the 8-h time-weighted limits they propose it is still possible for short-term transgressions to provoke other occupational health effects not considered by

their approach, namely asthma and rhinitis. For such effects appropriate limits can be derived only by systematic environmental monitoring linked to health surveillance (AGIUS, 1989).

(2) *Environmental monitoring strategy*

Where the assesment of health effects indicates the need, monitoring of exposure will be appropriate. Monitoring strategies for therapeutic substances are essentially the same as for other toxic substances (HEALTH AND SAFETY EXECUTIVE, 1989b). The environmental monitoring strategy to be used and the time weighting for the OELs must be relevant to the health effect and to the work practice. Thus, for example, if an acute adverse effect could result from a vessel-charging or de-traying procedure, monitoring exposure over short periods and establishment of a 10-min OEL would be appropriate. Acute adverse central nervous system effects include alteration of behaviour, sedation and loss of consciousness (e.g. benzodiazepines, opiates, tropic alkaloids). Acute effects on the heart or lungs may be brought about by substances such as beta-adrenergic agonists or antagonists, respectively. On the other hand if a chronic effect such as hormonal stimulation or suppression could arise from a continuous process, such as packing, monitoring on the basis of a full-shift OEL would be appropriate. The sampling technique needs to be relevant to the physical nature of the substance as well as to its health effect. Thus for a readily soluble therapeutic substance exerting effects outside the respiratory tract the inspirable dust fraction may be appropriate for sampling. On the other hand, a substance which could have localized pulmonary effects might have specific dust deposition fractions sampled (VINCENT and MARK, 1988).

(3) *Biological monitoring*

Biological monitoring or biological effect monitoring on their own will not provide the information necessary to derive OELs. However there may be circumstances in which pharmacological data already available can relate the risks of adverse health effects to blood levels of a therapeutic substance. It may be possble to measure occupational exposure in a particular workplace and carry out concomitant biological monitoring. This monitoring would then act as a bridge between exposure data on the one hand and known health effects on the other (HARRINGTON *et al.*, 1978a,b; BAXTER *et al.*, 1986). Thus if the sensitivity of the measurements permit it may be feasible to interpolate an OEL at which biological monitoring would indicate levels unlikely to produce a health effect.

(4) *Further health surveillance and exposure linkage*

This will be essential in many instances, for reasons already referred to. In addition, little is known about the potential occupational consequences of variations in the way individuals metabolize drugs, as for example in genetically-determined differences in acetylator or sulphoxidator status (FEELY and BRODIE, 1988). Moreover in an occupational context, exposure to a therapeutic substance may be accompanied by exposure to an intermediate which may compete for the same metabolic pathway or other mode of clearance. Therefore multiple exposures to chemically related compounds might dictate an *a priori* reduction of an OEL derived from single exposure assumptions. If this is not done, health surveillance techniques need to be in operation

in anticipation of such phenomena so as permit revision of the OEL. Similar arguments apply for pharmacodynamic considerations especially in relation to sensitization and other adverse health effects which are particularly relevant to occupational exposure.

Only systematic, prospective and appropriate health surveillance can provide adequate data on the magnitude and risk of health effects produced by known exposures. Occasionally these have been supplemented by volunteer simulation studies. As expected, there is no relation between therapeutic dose and the inhaled dose producing an adverse occupational health effect. Thus for example, calculations from published data suggest that in some individuals inhaled doses of Ispaghula can cause asthmatic symptoms even when three or four orders of magnitude lower than the therapeutic dose (GÖRANSSON and MICHAELSON, 1979; BARDY *et al.*, 1987). On the other hand, in the case of opiates, asthmatic symptoms may be provoked by inhaled doses one or two orders of magnitude lower than the therapeutic dose (unpublished data).

All quantitative studies of occupational health effects in relation to exposure to therapeutic substances should be designed on the assumption that an exposure–effect (or response) relationship will be demonstrable. Since OELs should be derived and applied in order to ensure that 'almost all' the population does not experience adverse effects on health (COSHH ACOP, paragraph 29) it follows that these studies should be carried out on all the workforce without preselection of substantial groups (such as atopics). The precautions that need to be taken in the use of routine monitoring or health surveillance data for epidemiological purposes have been discussed elsewhere (AGIUS *et al.*, 1988).

(5) '*Nuisance*' *standards*

Very few therapeutic substances that act on specific receptors are likely to warrant OELs as high as the 'nuisance' standard.

CONCLUSION

Any strategy for use in the derivation of OELs for therapeutic substances clearly involves investment in time, effort and money. However most of the components of it are, or should be, available 'on file' for pharmacological purposes (SARGENT and KIRK, 1988) or for the purposes of compliance with the COSHH regulations. It is hoped that with the coming into force of these regulations scientific accounts of the derivation of OELs for therapeutic substances will become more readily available. Recommendations could thus be made for OELs as defined by the COSHH regulations in Britain or equivalent legislation overseas. Other issues of a technical, social or economic nature may however influence the translation of these health-based limits into operational limits. These and other considerations may influence the above strategy or result in compromise (HENSCHLER, 1984). In any case OELs must be constantly under review so that they can be changed in the light of new knowledge about the substances concerned and their health effects.

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DISCUSSION

DR R. RAJAN (MOD, Navy): Production personnel handling therapeutic agents may be exposed to them over a long period. If these personnel became ill with a particular illness and if they were prescribed with the same sort of drug they handled at the workplace, what would be the effects of dose relations for treatment?

DR AGIUS: There are theoretical grounds as well as some occupational experience to suggest that significant exposures to therapeutic substances could cause 'down regulation' of the receptors for which they are specific and thus result in subsensitivity or tachyphylaxis (FREELY and BRODIE, 1988). This could conceivably manifest itself as a reduced response to therapeutic administration of that substance or in an adverse health effect. Thus for example one particular experience with occupational asthma could perhaps be explicable on this basis (AGIUS *et al.*, 1986). In some cases there may be evidence of allergic sensitization to a therapeutic substance as a result of occupational exposure to it. The individual and his general medical practitioner should be informed since such sensitization, if present, could constitute a contraindication to the subsequent therapeutic administration of the substance. I am aware of a few cases where this has happened.

MR A.J. CHAMINGS (Lothian Health Board): An illuminating analysis of an important field. Is it your impression that the approach you advocate is gaining wide acceptance among those creating and experiencing exposures, or is it the 'fraction of therapeutic dose' approach predominant?

DR AGIUS: The Control of Substances Hazardous to Health Regulations 1988 and especially parts of some of the paragraghs in the Approved Code of Practice (such as 3, 29 and 77) should be a useful ally in this respect.

MR ALVIN WOOLLEY (Consultant): To what extent do manufacturers pool information to allow standards of better quality to be derived?

DR AGIUS: Occupational physicians from a number of different pharmaceutical firms meet, or otherwise exchange information relevant to occupational health and hygiene. I understand the same can be said for occupational hygienists. The ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY (1985) has published a 'Green Guide' (see references) to provide broad guidelines. I do not know to what extent detailed information is pooled by different manufacturers.