



The Interdepartmental Group
on Health Risks from Chemicals

Draft Guidance Document “*Route-to-route extrapolation of toxicity data when assessing health risks of chemicals*”

The Interdepartmental Group on Health Risks from Chemicals (IGHRC) comprises representatives from 14 different UK government departments, research councils and agencies¹, and aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals. As part of its Forward Plan to 2006 the IGHRC agreed to produce a guidance document on route-to-route extrapolation of toxicity data.

The document outlines key factors that need to be considered in route-to-route extrapolations, together with criteria that should be met to enable confidence to be had in such extrapolations. Some generic recommendations are made which should help those involved in assessing the health risks of chemicals. The extent to which route-to-route extrapolations are currently used by different regulatory agencies in the UK is described in an Annex.

The first draft of the document was written by Dr Robin Fielder, with subsequent wide-ranging discussion at three Executive Committee meetings, and input from a number of other IGHRC committee members and their colleagues. This generated a fifth draft, which was circulated to a number of Expert Committees in April 2005. Unfortunately, we just missed the deadline for circulation to WATCH’s May meeting, but were informed that it would be discussed at your October meeting. We have since received feedback from ACHS, COT, ACP and EPAQS, and have updated the draft document to incorporate changes taking note of feedback from these four expert committees (Version 6.0).

As you will appreciate, a great deal of cross-departmental work has gone into the production of this draft and we are not seeking an extensive revision. Rather we are seeking feedback on any errors or essential missing material that needs to be brought to the IGHRC’s attention.

We are particularly seeking WATCH’s advice on a query raised by Dr Geoff Pigott, on behalf of EPAQS (see page 2). Dr Pigott has queried the document’s treatment of oral to inhalation exposures for relatively non-volatile aerosols, and wonders if the document is being too precautionary. He suggests changing the default factor for respirable absorption from 100% to 30% where there is moderate or low oral toxicity.

We are very grateful for WATCH’s advice and feedback.

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¹ BBSRC, Defra, Dept Health, DTI, Environment Agency, Food Standards Agency, Health & Safety Executive, Home Office, MHRA, Medical Research Council, NERC, Health Protection Agency, Veterinary Medicines Directorate, Pesticides Safety Directorate

Extract from letter to IGHERC from Dr Geoff Pigott, on behalf of EPAQS, received 13/7/2005

Re: IGHERC Draft Report – Guidelines on Route-to-Route Extrapolation of Toxicity Data

I am responding to your request for comment on this draft document on behalf of EPAQS.

Generally, this is a useful document. The limitations of route to route extrapolation are well explored and a set of rules for performing such extrapolations when necessary, should find wide application

My only major concern with this document related to the treatment of oral to inhalation exposures for relatively non-volatile aerosols. In this instance, the probability function inherent in the alveolar deposition of particulate matter is not taken into account. This has resulted in an excessively precautionary approach. This may be important only in so far as it may result in additional protection that is not warranted and thus divert resources from areas where they might be more efficacious. Although it is clearly preferable to be over conservative rather than the reverse, I think the approach can be modified to give a better representation of risk.

Figure 3.3.1 in the document provides a good illustration of the deposition efficiency of particles that are nominally respirable. This shows a peak alveolar deposition of approximately 50%, although many other publications put this peak somewhat lower. Given the spread of particle size in most aerosols, average deposition is generally at no more than 20%. It should be noted that, for the majority of respirable particles encountered in work places and in local exposure to dust and aerosols, the particle size range is generally within the 0.1–10 µm range with average deposition efficiency no more than 10%. In practice, many aerosols also contain substantial quantities of non-respirable material. The net effect is that the alveolar dose is relatively small when measured as a proportion of material in the atmosphere and even lower when the received dose is extrapolated from bulk material.

If we take a hypothetical chemical which consists entirely of mono-disperse 1.0 µm particles and disperse it in air, only 20% of the total dust in this atmosphere will deposit in the alveolar region. Of the remainder, the vast majority will be cleared via the mucocilliary system and subsequently swallowed. The possibility that some may be absorbed in the conducting airways cannot be eliminated but it is highly unlikely that this absorption efficiency will reach anything close to that seen in the gastro-intestinal tract. Thus, for a nominal 10 mg exposure under these circumstances, approximately 8 mg will in effect be an oral exposure and only 2 mg available for absorption via the lung. Simple application of the 10/100% default values shows that a differential factor of 3 is adequate to account for any potential increased absorption in the lung, rather than the 10 fold factor adopted. This differential is, of course, much greater for coarser particles, which are more likely to be encountered in industrial circumstances. Finer particles may predominate under some circumstances, especially in background environmental exposures: these may warrant differential treatment.

The above may be mitigated by the method in which the atmosphere is measured. Where a 'respirable' sampler is used this applies a correction for the above and it is reasonable to use the value directly. However, most modern systems tend to use a measurement of total dust plus measures of particle size distribution as these allow for corrections of the differential respirability between species.

This is a complicated area. I believe it deserves additional consideration in this document.