



R&D Briefing

Examining Endpoints

High Dose Selection for Carcinogenicity Studies

Number of carcinogenicity studies initiated by companies participating in survey

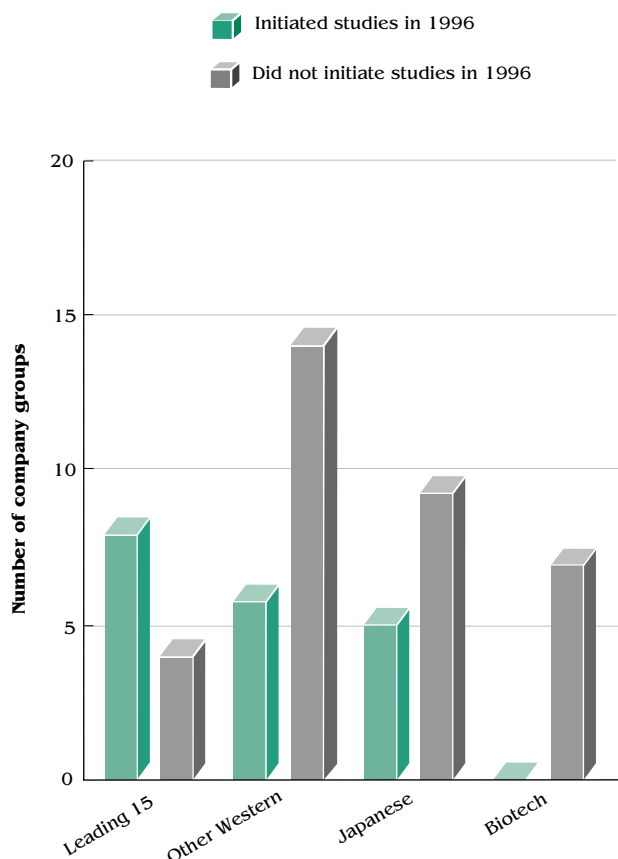


Figure 1 Companies initiating carcinogenicity studies during 1996 were predominantly in the leading 15 (grouped by R&D expenditure in 1996). Of the 39 companies that responded to requests for information in both stages of the survey (1995 and 1996), 18 did not initiate carcinogenicity studies over that two-year period.

- ICH guidance on dose selection for carcinogenicity studies, finalised in late 1994, advocates flexibility and proposes alternatives to the maximum tolerated dose (MTD), the traditionally accepted endpoint.
- Have companies adopted this flexible approach? Which endpoints are most frequently chosen, and why? Are alternatives applicable to the majority of compounds? Have industry practices changed in the past year?
- The second CMR International survey monitoring implementation of the ICH guideline shows that the MTD is still regarded as the standard endpoint for high dose selection. Data from 49 carcinogenicity studies reveal that, during 1996, there was little increase in the use of alternative endpoints over the previous year.

Perspective

Findings from the second CMR International survey monitoring the implementation of the ICH (International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use) guideline on high dose selection for carcinogenicity studies, reveal industry practices during 1996. In addition to identifying endpoints used as the basis for high dose selection, as previously, this recent survey also probes the reasons for the choice of endpoint.

Fifty-three companies (82% of those approached) responded to the initial request for information; of these, 34 had not initiated any carcinogenicity studies during 1996 (*Figure 1*) and so were excluded from further analyses. Of the remaining 19 companies all but one subsequently returned completed questionnaires relating to 49 carcinogenicity studies for a total of 32 compounds.

Underlying Issues

The traditional endpoints for high dose selection in rodent carcinogenicity studies are maximum tolerated dose (MTD), generally based on the results of three

month toxicity studies, and maximum feasible dose (MFD). For compounds of low toxicity, the large doses needed for such testing can cause alterations in physiological function and tumours that may be of little relevance to clinical usage.

The ICH guidance sought to provide a more flexible approach to high dose selection, proposing that pharmacokinetic, pharmacodynamic or saturation of absorption endpoints could be acceptable. However, the pharmaceutical industry has expressed concern that these alternative approaches, in particular the use of the 25-fold ratio of rodent to human plasma AUC (area under the plasma concentration-versus-time curve), are not applicable to the majority of compounds investigated.

Approaches Adopted

For carcinogenicity studies initiated in 1996, the new approaches to high dose selection were used for only 24%. The majority were based on the traditional endpoints, MTD and MFD; in a few studies, two or more endpoints were used.

These findings reflect little change over the previous year in the choice of endpoint (*Figure 2*). Studies initiated in 1995 may have been designed before the

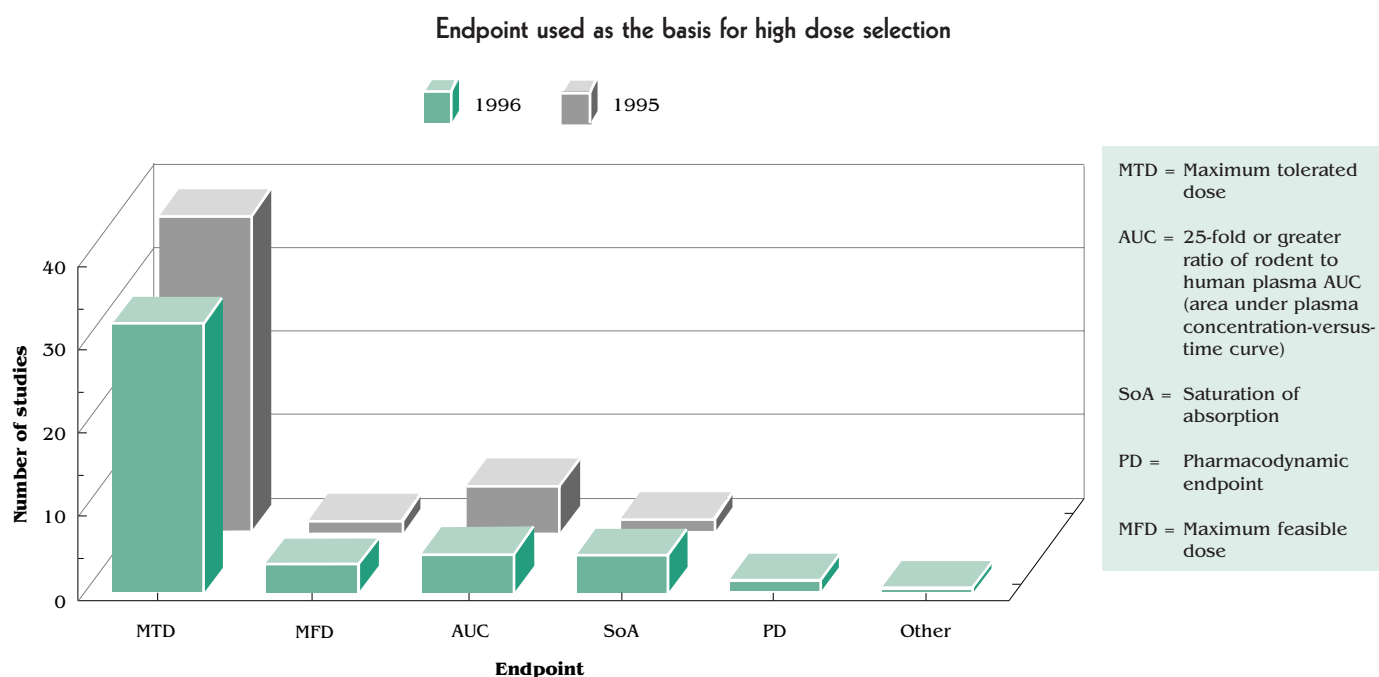


Figure 2 There was little change in industry practice between 1995 and 1996 in the endpoints used as the basis for high dose selection for carcinogenicity studies initiated in each year.

guideline reached Step 4 of the ICH process and therefore there was potential for an increase in use of the new endpoints in 1996. Some of the factors underlying the lack of change in industry practice can be discerned from the following considerations.

Why does MTD predominate?

The maximum tolerated dose was chosen as the endpoint for high dose selection for a number of reasons (Figure 3). Principal among these is the difficulty in using a 25-fold rodent to human plasma AUC ratio, either because such a ratio is unattainable, or because the dose required to achieve such a ratio is equal to or larger than that required for the MTD.

The results presented in Figure 3 also suggest that some regulatory authorities solely support the use of the MTD for high dose selection. Specific regulatory requests or perceived regulatory expectations were the reasons behind six studies, conducted by four companies.

Can acceptable AUC ratios be achieved?

For the rodent to human plasma AUC ratio to function as an endpoint it must equal or exceed 25. Therefore, to

assess its potential usefulness, respondents were asked to provide values for the rodent to human AUC ratios achieved, regardless of the endpoint used. Such information was available for 30 studies on 19 compounds. In nine studies (30%) an AUC ratio of 25 or greater was achieved in both males and females (Figure 4); this corresponds to 37% of the compounds tested. In only four of these nine studies was the AUC ratio used as the endpoint. For two studies, MTD was used as the endpoint due to perceived regulatory expectations. Saturation of absorption was used as the endpoint for the remaining three studies.

The rodent AUC will be reassessed during the course of a carcinogenicity study by only two of the four companies that used AUC ratio as the sole endpoint for high dose selection during 1996.

Future Perspective

The MTD still appears to be regarded as the standard endpoint for high dose selection; the difficulty in achieving a 25-fold rodent to human AUC ratio is a major factor behind this. A reduction from the 25-fold AUC ratio currently specified in the ICH guideline would

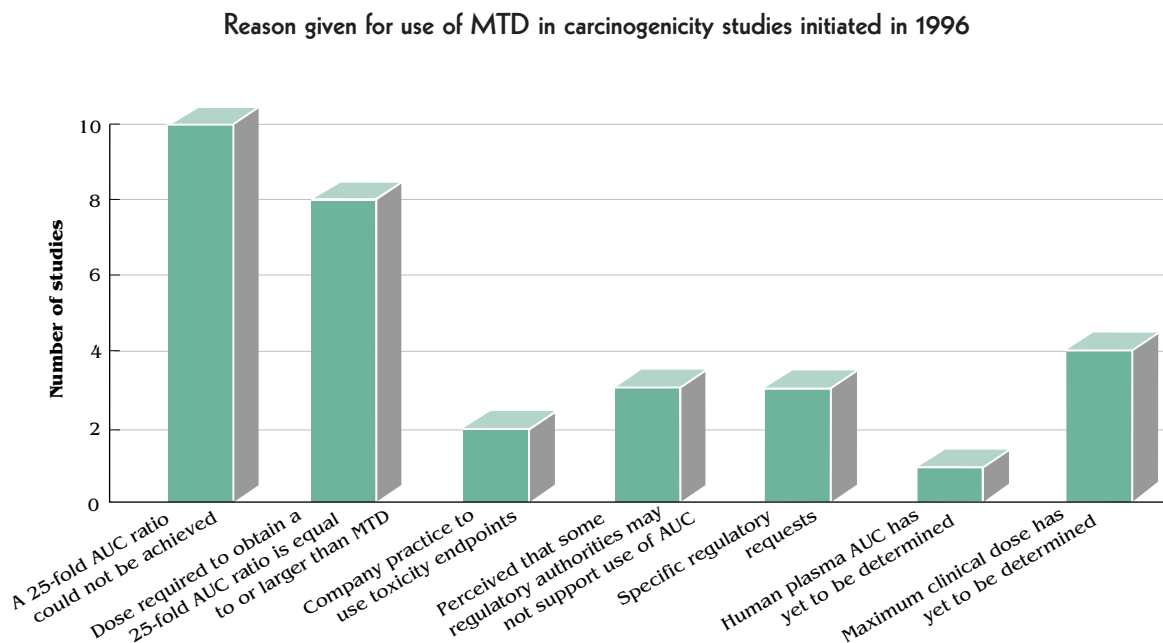


Figure 3 Reasons for the choice of endpoint for high dose selection were provided for all but one of 32 studies in which MTD was used. For 58% of these studies, an AUC ratio of 25 could not be achieved, or the dose required to obtain a 25-fold AUC ratio was equal to or larger than the MTD.

Rodent to human AUC ratios achieved

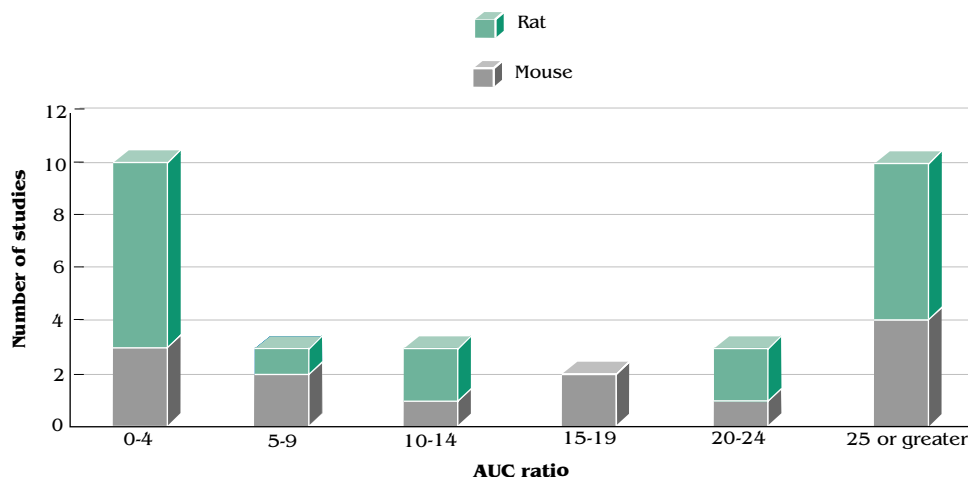


Figure 4 In nine of 30 studies (30%) conducted on 19 compounds a rodent to human AUC ratio of 25 or greater was achieved in both males and females. For one rat study, different AUC ratios were achieved in males and females. Both ratios have been included in the above graph.

make this pharmacokinetic endpoint applicable for more compounds; whether this is justified scientifically will become more apparent when further experience with the use of this endpoint is gained. The apparent reluctance of regulatory authorities to support alternative approaches to high dose selection reported by respondents, and the reluctance on the part of industry to challenge perceived regulatory expectations, must also be overcome if further implementation of the guideline is to occur.

References

ICH Guideline 'Carcinogenicity: Guidance for dose selection for carcinogenicity studies of therapeutics'. Federal Register (01/03/95) Vol.60 No. 040, Part XII.

CMR International Report: High Dose Selection for Carcinogenicity Studies of Pharmaceuticals Initiated in 1995.

G A Ashton, S A Griffiths, J A N McAuslane & C E Lumley. CMR96-65R, September 1996.

Copies of the full report, "High Dose Selection for Carcinogenicity Studies: Implementation of the ICH Guideline During 1995 and 1996" which contains 48 pages, 16 figures and tables, and 2 appendices, can be obtained at a cost per copy of:

Non-sponsoring organisations	£500
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These can be ordered, quoting reference number CMR97-65R2 from Shaida Dorabjee, Research Services Manager, at Centre for Medicines Research International.

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