



# R&D Briefing

## Predictive Potential

### Industry Strategies for Carcinogenicity Testing

Company involvement with alternative models

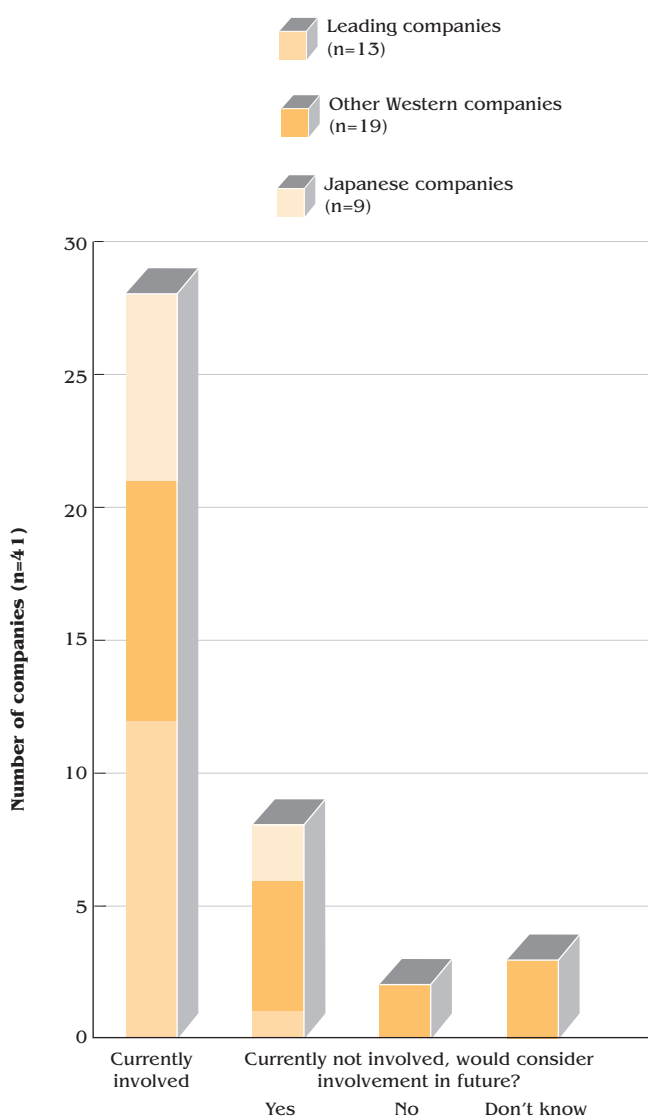


Figure 1 Twenty-eight of the 41 companies that participated in this survey were involved with originating, developing or evaluating short- or medium-term *in vivo* rodent models, at the time of the survey. Of these 28, 23 were participating in the ILSI (International Life Sciences Institute) research programme.

- *The non-clinical testing of pharmaceuticals should generate information that is both useful and relevant to likely future human use. This ideal is not easy to achieve. Criticism concerning the value of long-term carcinogenicity testing in two rodent species led ICH to recommend that a single long-term study might be better complemented by a short- or medium-term *in vivo* study.*
- *Have these recommendations found wide support? Is the industry adopting new strategies for the assessment of carcinogenic risk in humans? Do the recommended new models generate relevant information? Is that information being used in regulatory submissions?*
- *The answers to these questions, as revealed by a CMR International survey of pharmaceutical industry experience with alternative models for carcinogenicity testing, are fairly tentative at present. A clear path to reduce reliance on the conventional long-term study has yet to be determined.*

## Perspective

The relevance of findings from the conventional long-term rodent carcinogenicity study to the assessment of human risk has come under critical evaluation in recent years. In particular, concern has been raised about the scientific justification for conducting long-term carcinogenicity studies, or bioassays, in two rodent species. Such studies have traditionally formed the backbone of carcinogenic risk assessment and therefore have been a worldwide regulatory requirement for human pharmaceuticals for which an assessment of carcinogenicity is required.

In view of these concerns, the International Conference on Harmonisation (ICH) developed a guideline which advocates a more flexible approach to carcinogenicity testing. In particular, it proposes that in place of a second long-term carcinogenicity study, a short- or medium-term study in an *in vivo* rodent model may be appropriate.

## Study Details

More information is needed on current levels of industry experience with, and opinion on, these new models before companies can determine future strategies. On this premise, CMR International conducted a questionnaire based survey of 26 companies known to be participating in the International Life Sciences Institute (ILSI) programme to evaluate alternative models, and 40 companies that were not. Forty-one companies (62%) responded.

## Involvement

Twenty-eight of the responding companies were involved with either originating, developing or evaluating short- or medium-term *in vivo* rodent models (Figure 1). Of these, 23 were participating in the ILSI programme. A number of reasons underlie this involvement, including the potential scientific benefit to be gained,

Company strategy for the assessment of carcinogenic potential for regulatory submissions

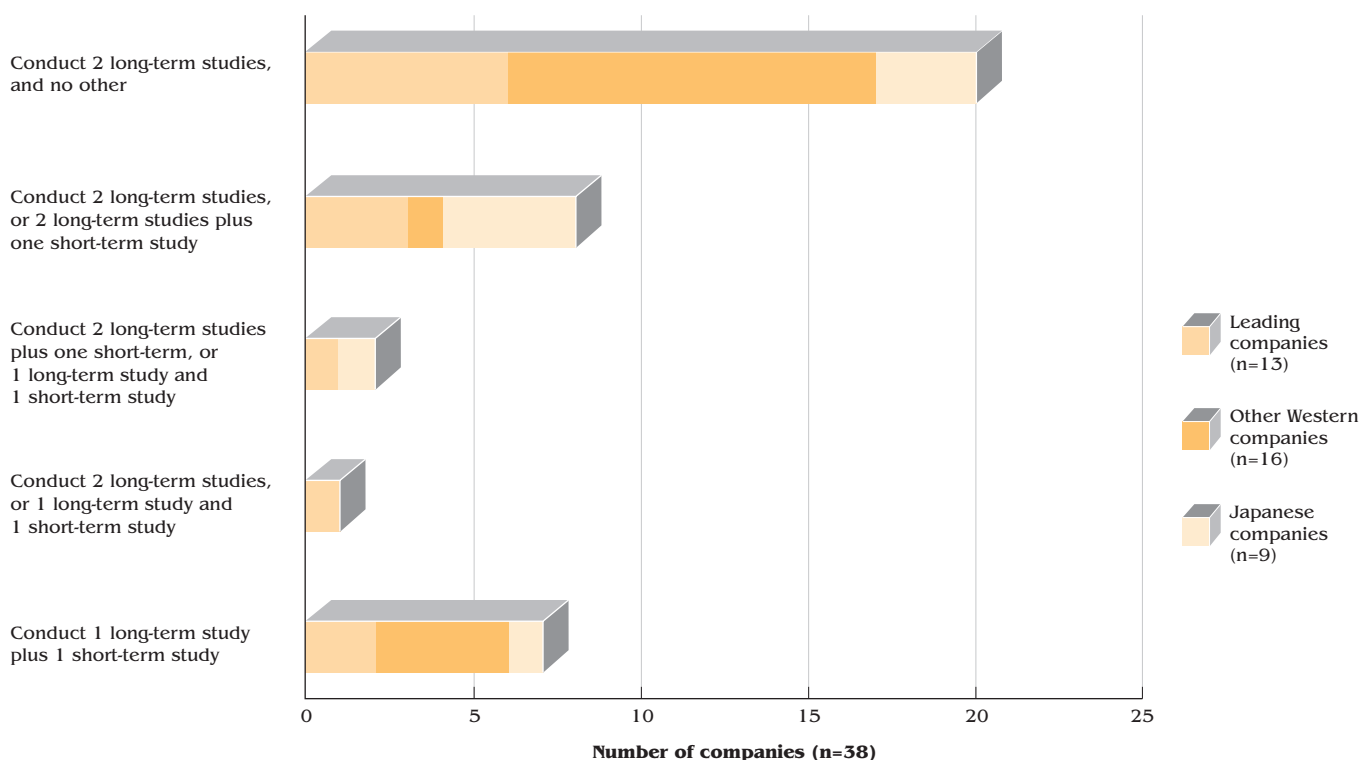


Figure 2 The strategy of 18 companies for assessing carcinogenic potential to support regulatory submissions included the conduct of short- or medium-term studies in rodent models, either in addition to two long-term carcinogenicity studies, or in place of a second long-term carcinogenicity study. Twenty-eight companies continued to conduct two long-term carcinogenicity studies, of which eight would also consider conducting a study using an alternative model.

### Company experience with short- or medium-term *in vivo* rodent models

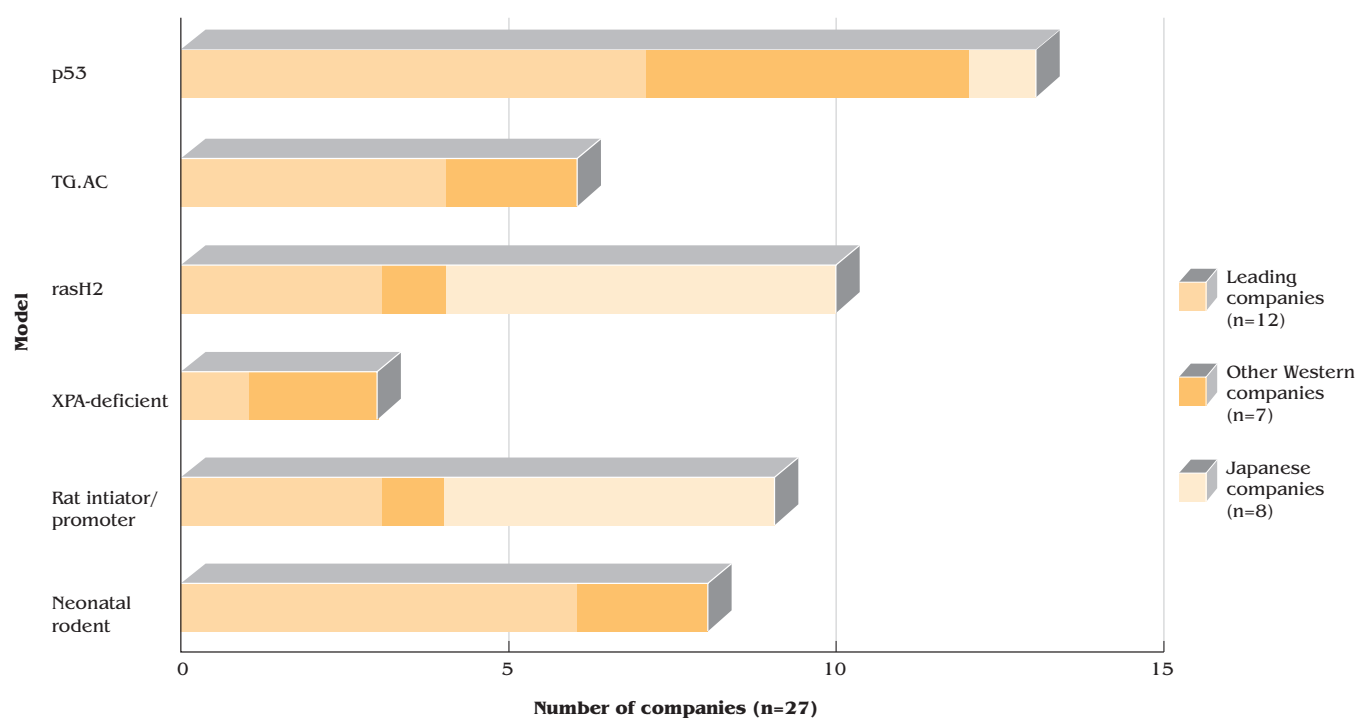


Figure 3 A regional bias in terms of the types of models with which companies have experience is evident. A greater number of Western companies have experience with the p53-deficient mouse, while more Japanese companies have experience with the rasH2 and rat initiator/promoter models.

and the possibility of regulatory requests for such information. An increase in regulatory support for the use of alternative models would encourage six of the remaining 13 companies to reconsider their current lack of involvement.

### Assessment Strategy

Long-term studies dominate the strategy for assessing carcinogenic potential to support regulatory submissions (Figure 2) in 28 companies; eight of these would also consider, on a case by case basis, the use of an alternative model. However, for 18 companies the strategy already includes short/medium-term studies, with seven conducting them in place of a second long-term carcinogenicity study.

It would appear that more information is required before companies are prepared to change their strategy. Many respondents indicated that they await results from the ILSI programme, while others need more insight into the regulators' interpretation of data from alternative models.

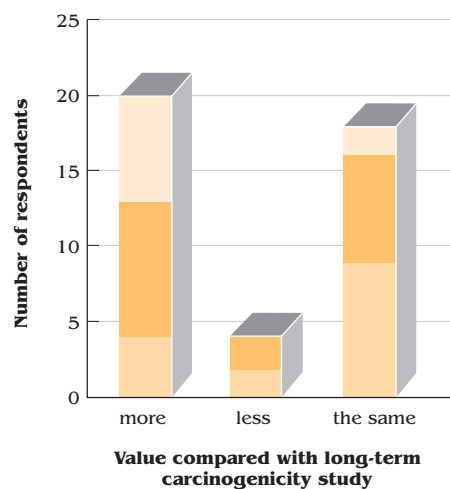
### Which 'Alternatives'?

A variety of models are under investigation for their potential to generate information that is relevant to the detection of carcinogenic risk to humans. Of particular concern is reliable prediction of non-genotoxic carcinogenesis. Relatively new techniques based on transgenic technology (such as the rasH2 transgenic mouse) are being tested alongside the rodent initiator-promoter and neonatal rodent tumorigenicity models that have been in existence for many years.

Twenty-seven companies provided details of their experience with one or more short- or medium-term *in vivo* rodent model (Figure 3), with the heterozygous p53<sup>(+/-)</sup> deficient mouse model being used most often. There appears to be a regional bias in the pattern of experience, which may reflect regional differences in the availability of the models. At the time of the survey, breadth of experience was limited; the majority of companies (77%) had accrued experience with only one or two models, although six companies had worked with three or four.

## Respondents' opinion of potential value of alternative models for providing scientifically relevant information for the assessment of human carcinogenic risk

a) for genotoxic compounds



b) for non-genotoxic compounds

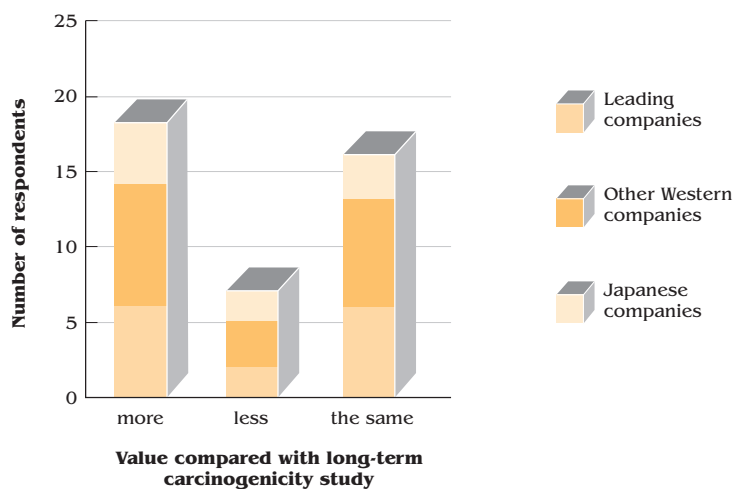


Figure 4 The respondents were almost equally divided in number between those that believe that short- or medium-term *in vivo* models may provide more scientifically relevant information than the long-term carcinogenicity study, and those that believe alternative models will provide the same amount or less information than the long-term carcinogenicity study.

### Opinions Differ

Opinions vary as to whether the short- and medium-term models currently under investigation are likely to provide information that is more scientifically relevant to the assessment of human risk than the traditional long-term carcinogenicity study (Figure 4). The pattern of answers was similar for those with experience, and those without experience, of the new models.

The majority (83%) expect studies with the new models to be both cheaper and less time consuming than long-term carcinogenicity testing.

### Early Days

Industry experience, outside that gained through the ILSI programme, with short- or medium-term *in vivo* rodent models for assessing human carcinogenic risk is fairly limited. Until the benefits and limitations of these models are fully understood, their role in regulatory decision making should remain under scrutiny.

A copy of this R&D Briefing is available on the CMR International web site. Additional paper copies can be obtained free of charge from the Centre.

Copies of the full report, "Industry Experience with Alternative Models for the Carcinogenicity Testing of Pharmaceuticals", which contains 79 pages, 19 figures and 7 tables, and 3 appendices, are available **free of charge to CMR International Sponsoring Companies**. The report can be ordered quoting reference number CMR99-98R.

Copies of the full report are also available in electronic format for Sponsoring Companies. For further details please contact CMR International.

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