

The International Symposium on Regulatory Testing and Animal Welfare: Recommendations on Best Scientific Practices for Acute Local Skin and Eye Toxicity Testing

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Introduction

Breakout Group 1 addressed the current best practices and the future possibilities for acute local toxicity testing—skin and eye. Participants in the group (listed at the end of this report) had previously reviewed a number of key background references (also listed at the end of the report), which the group's leaders had selected before the meeting. They were asked to consider the questions described below as part of their general discussion.

Current Considerations

1. How important clinically is skin and/or eye irritation caused by chemicals and products?
2. Is sufficient attention paid to predicting human effects, rather than whether something is irritating to the rabbit?
3. How widespread is the use of prescreens and stepwise approaches to skin and eye irritation?
4. Are *in vitro* alternatives used extensively in product selection by industry? If so, is this in-house experience being shared and used to improve the methodology or interpretation?

Future Improvements

1. Should the development and validation of alternatives for skin and eye irritation be concentrated on those chemicals and products of greatest clinical concern (e.g., surfactants and personal care products)?
2. What do we understand and not understand about the biological mechanisms whereby chemicals cause local irritation?

3. What is the prospect of wider use and acceptance of human testing for skin irritation potential?
4. How quickly will the Organisation for Economic Co-operation and Development (OECD¹) and National Regulatory Guidelines begin to reflect best practices fully, such as the use of validated skin corrosion tests and new stepwise approaches to skin and eye irritation testing?

Report on Group Discussions

Current Best Practices

In attempting to answer the questions, the breakout group tried to maintain a focus on the major objectives of the Symposium: to develop or identify best practices to minimize or eliminate pain and distress for animals used in safety evaluation and testing procedures; and to improve communications among regulated industry, animal welfare enforcement authorities, and regulatory authorities that require safety evaluations of toxicity testing.

It was agreed that the clinical importance of skin and eye irritation does vary between product categories, especially for the consumer. Materials that are corrosive or severely irritating are unlikely to be in consumer products or other products with widespread use and potential for exposure. However, for these types of products, it is particularly important to use predictive models that permit reasonably accurate discrimination between nonirritants and materials that could cause mild to moderate effects on human skin or eye. All types of products and chemical substances are potentially hazardous in the context of occupational exposure, and the rank order of concern is eye corrosion, skin corrosion, eye irritation, and skin irritation.

The group spent considerable time discussing the validity and relevance of the rabbit models currently used for predicting human skin and eye irritation. Significant ana-

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¹Abbreviations used in this report: ECVAM, European Centre for the Validation of Alternative Methods; ICCVAM, Interagency Coordinating Committee for the Validation of Alternative Methods; OECD, Organisation for Economic Co-operation and Development.

tomical and metabolic differences, for both the eye and skin, between the human and the rabbit, could lead to different responses to an irritant substance. Breakout group participants were concerned that the effect of these basic differences, in terms of the predictability of the rabbit for human response, could be exacerbated by certain aspects of the methods detailed in OECD guidelines 404 (skin) and 405 (eye). They expressed particular concern about the following: in eye studies, the use of local anesthetics, which can exacerbate injury; the use of irrigation of the rabbit eye; and the meaning and use of “semioclusive” dressings for skin irritation studies.

The group noted the widespread use of prescreening for skin and eye irritation testing. However, the group agreed that the approach used is not necessarily identical to the stepwise approach recommended either in the OECD guidelines or in the Globally Harmonised System for classification. These testing strategies are successful only if a sufficiently comprehensive database is available to guide the individual(s) carrying out the tests. Typically, access to these types of databases is not available to contract laboratories. As much information as possible should be made available to laboratories commissioned to conduct skin/eye irritation studies, given that although some algorithms for structure-activity relationships are available, there are few such systems with validated prediction models. At the present time, the use of structure-activity relationships is of questionable utility.

In vitro alternatives are used extensively in product selection by industry; however, generally speaking, most in-house experience is not being shared across the industry. Therefore, it is difficult to obtain the necessary information to improve methodologies or to help with the interpretation of results. The group expressed a desire to encourage publication of more information by regulatory agencies and industry; and to encourage the use of in vitro technology through training workshops. Education and training are critical to the spread of information throughout the appropriate communities. Currently there appears to be a shortage of in vitro testing facilities outside the realms of industry or government laboratories.

Future Improvements

The group recognized the need for better ways to develop and validate alternative methods for skin and eye irritation. Currently the emphasis is on personal care products and surfactants, but this should be expanded so that the broadest possible number of chemical classes are included. Large-scale validation studies have not proved successful in the past, therefore the group expressed the belief that validation efforts should be concentrated on smaller, focused studies with specific objectives. Industry can contribute to these efforts by sharing data and by being involved in technology transfer of protocols. A major concern of the group was the current lack of availability of chemicals with appropriate in vivo data and of known purity/composition.

Current understanding of biological mechanisms whereby chemicals cause irritation is limited; however, research into these mechanisms is under way. It was the consensus of the group that although there are several mechanisms involved in local skin irritation, it may be feasible for a single test to predict many of the mechanisms and hence, their clinical effects. A number of promising methodologies are on the horizon, in particular, reconstituted human skin models. In the case of the eye, it is more difficult to imagine a single in vitro test replacing the rabbit because there are at least three tissues involved—the cornea, the conjunctiva, and the iris. A test for predicting corneal damage and a separate procedure for predicting conjunctival damage may, in combination, be able to predict the majority of eye irritants. Such tests should be validated against individual tissue scores from Draize tests. An ability to demonstrate the speed and degree of recovery would be highly desirable in any in vitro alternative method.

Good prospects for wider use and acceptance of human testing for skin irritation exist in most countries. However, human testing should be approached carefully. When chemicals or products are shown to be nonirritating in vitro and when human exposure is intended (e.g., for personal care products), it is acceptable to proceed with human patch testing, as long as all ethical issues are considered. The Helsinki guidelines have removed the requirement for performing in vivo animal studies before human studies, but appropriate background information is still required. There are a few countries in the European Union where human testing remains an issue. The group considered that the OECD Draft Guideline for acute dermal irritation in human volunteers appears somewhat aggressive, and they recommended its revision.

Finally, the breakout group recognized a lack of harmonization between the United States and the European Union regarding acceptance of validated studies. These differences are currently being addressed, and harmonization should occur within a reasonably short period of time. Protocols that have been validated by the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM¹) and by the European Centre for the Validation of Alternative Methods (ECVAM¹) appear to be reasonably quickly accepted by national regulatory authorities, but acceptance appears to be faster in the European Union than in the United States. The group felt strongly however, that validation should remain with ICCVAM and ECVAM and not be a function of the OECD.

Recommendations

- Use predictive models capable of discriminating between nonirritant products and products that can cause mild to moderate effects on human skin or eye.
- Redraft the OECD Guidance Document to accompany OECD guidelines 404 and 405, to address a number of ambiguous areas, in particular:

Use of local anesthetics,
Irrigation of rabbit eye,
Use of semioclusive dressing, and
Optimization of prediction of human skin/eye
irritation from the rabbit model.

- Make available to any laboratory, commissioned to conduct local acute toxic effects studies, all available structure activity relationship data and skin/eye effects of similar chemicals.
- Encourage the US Environmental Protection Agency to publish more information (e.g., data on high-production-volume chemicals).
- Conduct hands-on workshops on in vitro technologies.
- Encourage the establishment of in vitro testing facilities outside of industry and government laboratories.
- Encourage validation studies to be concentrated on small focused studies with specific objectives.
- Encourage industry to share data, in particular, to permit in vivo/in vitro comparisons and to establish standard reference banks of chemicals.
- Encourage industry to become more involved in technology transfer of protocols.
- Revise the OECD draft guideline for acute dermal irritation in human volunteers.
- Encourage ICCVAM and ECVAM to be responsible for validation, which should not become a function of OECD.
- Work toward harmonization of the process for acceptance of validated protocols between the United States and the European Union.

Background References

Skin

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