A Successful Peer Review Program for Regulatory Decisions

KENNETH D. FISHER

Life Sciences Research Office, Federation of American Societies for Experimental Biology, 9650 Rockville Pike, Bethesda, Maryland 20014

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A unique peer review program for Federal agencies has been operating since 1962 to provide opinions of leading investigators for sponsors in various fields of the life sciences. The most notable study has recently been completed for the U. S. Food and Drug Administration on the Generally Recognized as Safe (GRAS) food ingredients. Over 400 substances were evaluated by a Select Committee over a 10-year period and evaluative reports were submitted to the regulatory agency. Based in part on these reports made available for public comments, the FDA has been able to develop decisions for appropriate actions on the health aspects of these food ingredients. A comprehensive report on the work of the Select Committee on GRAS substances will be published in the archival literature.

In March 1972, The Federation, through its Life Sciences Research Office (LSRO), organized the Select Committee on GRAS Substances for the purpose of assisting FDA in the evaluation of scientific information on the presence or absence of adverse health effects associated with those GRAS substances other than flavors, spices, and essential oils. This step, a decade ago, was taken with some reluctance and apprehension by the Federation.

In March 1982, with little reluctance and with some rejoicing, the Select Committee completed this task. During the 10-year period, the Select Committee prepared 141 reports and several supplemental reports on 468 substances considered GRAS or prior-sanctioned food ingredients.

Of the 468 substances considered, 422 were evaluated for direct addition to foods and the remaining 46 were evaluated only as components of packaging materials. The Select Committee devised, with FDA concurrence, five conclusions for their scientific opinions, which are stated briefly in Table 1.

The five substances viewed with some concern were acetylated distarch glycerol, distarch glycerol, hydroxy propyl distarch glycerol, succryl distarch glycerol, and sodium chloride. In addition, the Committee did give a No. 4 conclusion for calcium lactate and lactic acid [D(-) and DL] for use in infant formulas.

TABLE 1
CONCLUSIONS OF THE SELECT COMMITTEE ON 468 GRAS SUBSTANCES

1. No evidence of adverse health effects—continue as GRAS.

2. No evidence of adverse health effects, but additional data necessary if increased or new uses are contemplated—continue as GRAS with limitations on use.

3. No evidence of adverse health effects, but uncertainties exist—issue an interim food additive regulation requiring that testing be undertaken, but continue GRAS status until such tests are completed and evaluated.

4. Evidence is insufficient to determine if reported adverse health effects are not deleterious—require safe conditions of use be established.

5. Inadequate data on biological studies precludes evaluation—invite submission of data or, if none received, rescind GRAS status.

Of the 468 substances evaluated, the Select Committee concluded:

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<td>339 (72%) were No. 1</td>
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<td>69 (15%) were No. 2</td>
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<td>21 (5%) were No. 3</td>
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<td>5 (1%) were No. 4</td>
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<td>34 (7%) were No. 5</td>
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Having completed the actual GRAS Review process, the Select Committee is currently focusing its final efforts on the completion of a second “White Paper,” following up the one published in 1977 (Siv et al., 1977). This second effort, entitled, “Insights on Food Safety Evaluation” extends the thoughts of the Select Committee, within the limitations of their 10 years of experience with GRAS food ingredients, in four areas addressed in the first “White Paper.” These are:

1. The range of factors to be taken into consideration in the safety assessment of a food ingredient;

2. Estimates on the state of the art and commentaries on the nature of the technical complexities that are encountered and are perplexing in the business of rendering scientific judgments on food safety;

3. Suggestions concerning the philosophical, procedural, and scientific ramifications of such a process of safety evaluation; and,

4. Research needs related to improvement of the validity of data necessary to undergird the scientific evaluation process.

This second “White Paper” will be completed by December 1982, at which time it will be published and will be widely available. The Select Committee, with appropriate toasts, ruffles, and flourishes, will cease to exist in all but memory, leaving only its written record.

The concept of peer review and organization of expert panels evaluating scientific issues is very much an activity of LSRO and the Federation. We anticipate that the Federation will undertake similar evaluation efforts in the future, utilizing the lessons learned in the decade of experience with the Select Committee, as appropriate.

Several aspects of the Select Committee’s operation and activities contributed to the successful completion of this effort. Some are minor, others major; some relate to administration and management, some scientific; and others clearly relate to human factors. All in all, they have been facets of the GRAS review experience.
(A) In regard to the Select Committee itself:

—its members possessed an acknowledged reputation for scientific endeavor;
—its members represented the multidisciplinary mix necessary to evaluate a multiplicity of health effects of food ingredients;
—its members recognized the need to seek outside expertise as required;
—its meetings were conducted in both open and closed sessions depending on the meeting purpose;
—its meetings were conducted with total absence of the adversarial process;
—its members were aware of and acknowledged the issue of conflict of interest;
—it established procedures to collect data from all sources, thus supplementing the scientific literature reviews supplied by FDA; and,
—it consisted of a unique mix of individuals with remarkable perseverance and motivation.

(B) In regard to LSRO and the Federation, it was sufficiently flexible, persuasive, foresighted, or plumb lucky to:

—seek and receive from FDA complete freedom to appoint members of the Select Committee and LSRO scientific staff based upon Federation policies and procedures, without interference or approval;
—instilute and maintain a posture with regard to conflict of interest for both Select Committee members and LSRO staff that was both more rigorous than that of the government, and subject to internal Federation review;
—make provision for adequate support staff for managerial and administrative activities;
—make provision for adequate scientific staff who provided continuity in evaluation of specific substances, who were accepted by the Select Committee members as partners in the activity, but who maintained a total separation from development of the Select Committee’s scientific opinions;
—institute a procedure for an internal higher level of review that focused upon scientific objectivity and completeness of Select Committee reports; and,
—build a relationship with FDA scientific staff that was grounded in mutual respect and regard for the boundaries of an external organization making evaluations on scientific data and an internal structure that had a responsibility to reach regulatory decisions on the basis of a broad array of factors, of which science was but one.

(C) Finally, in regard to the overall framework of the Select Committee’s activities and the Federation’s actions in the GRAS review process, perhaps the most important aspect was the clear separation of scientific evaluation from regulatory decision making.

The nature of questions to be presented to an external panel of scientists should be carefully considered by the government agency prior to submission. An appropriately constituted external scientific panel can be expected to challenge regulatory constraints on their interpretation of scientific facts or generally accepted hypotheses. For example, induction of cancer has one definition in the regulatory sense, but has a broader meaning in relation to processes of oncogenesis. Thus particular attention must be directed to phrasing of questions of science apart from addressing aspects
of regulation. Scientists can evaluate available data and can distinguish the scientific information most applicable to questions identified by the agency. However, extension of scientific opinion to regulatory interpretation should remain an agency prerogative. Further, separation of the evaluation process from weighing of scientific considerations in the regulatory process provides opportunities for special interest groups to bring additional viewpoints to bear on the ultimate decision-making process.

In the early stages of the GRAS evaluation effort, the Select Committee identified a need to have alternative conclusions that would be applicable to the majority of situations which might arise in the evaluation process and at the same time would provide FDA with unambiguous statements for each substance reflecting the consensus of the Select Committee regarding health aspects of the use of that food ingredient. Based in part upon discussions with FDA, the Select Committee adopted the five conclusions described previously, and one or another of them was used by the Select Committee for all but a very few of the several hundred substances evaluated.

There are several advantages in proceeding in this manner. First, the evaluation panel acknowledges a responsibility to decide which of the conclusions best fit the available information concerning a substance. While this was difficult in many cases and was not possible in a few, the Select Committee did provide FDA with evaluative opinions based on available scientific information. Thus the Select Committee avoided the tendency of cautious scientists to always require high-quality or complete data and, in the absence of such data, to "write around" and reach no useful conclusions. Second, FDA, in developing reaffirmation decisions and in considering modifications or new regulations, experienced less difficulty in interpreting the Select Committee's conclusions. Third, the repetitive use of alternative conclusions provided the scientific community, industry, and the general public with a relatively concise indication of the Select Committee's evaluation of available scientific evidence of hazard or safety.

Finally, if the 10 years of experience of the Select Committee and the Federation has done anything worthy of posterity, it has provided a framework of a scientific evaluation process which has successfully:

—maximized the opportunity to ensure gathering of all relevant scientific data;
—minimized the chances for subconscious and indirect biasing of conclusions; and,
—ensured that a permanent record of the evaluated data and scientific opinions are provided as a public resource.

REFERENCE