GLOBAL FOOD SUPPLY

Reevaluate Pesticides for Food Security and Safety

Generic pesticides, vital in the developing world, present assessment challenges.

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With global population projected to increase above 9 billion by 2050, food security—the availability of food and one's access to it—is increasingly important (*1*). Crop-protection products can help reduce yield losses caused by pests, pathogens, and weeds, to help feed the world's population sustainably. Given potential harm for human health and the environment, regulation of pesticide use in agriculture has been controversial.

Although most pesticides are developed and patented by large multinational companies, ~30% of total sales are by producers of generic versions (*2*). For these chemicals, the initial name-brand producer is often no longer interested in commercialization or in investing resources to generate updated toxicological data critical for sponsoring international health impact assessments (see below). But cheaper, generic compounds are necessary for developing countries to increase their food production, feed their population, and trade internationally.

Without a committed sponsor of assessments for generics, sufficient data may not be available to update their safety assessment. Thus, ~30% of pesticides marketed in developing countries, with an estimated annual market value of U.S. $900 million, may not meet internationally accepted criteria for safe pesticide residues in the food supply (*3*). They could pose unacceptable dietary risk to human health, with repercussions for food security, safety, and trade that could disproportionately affect developing countries (*1*). We discuss an approach to address this.

International Scientific Risk Assessment

The *Codex Alimentarius* Commission (CAC) of the United Nations' Joint Food and Agricultural Organization–World Health Organization (FAO-WHO) Food Standards Programme is recognized by the World Trade Organization (WTO) as the normative body to produce international science-based standards (e.g., for food hygiene), guidelines (e.g., for safety assessment of food derived from biotechnology), and codes of practice (e.g., for fish and fishery products) that are used in case of trade disputes involving sanitary or phytosanitary considerations (*5*). *Codex* involves 185 member countries (99% of the world's population). *Codex* standards protect public health in developing countries that lack infrastructure for proper national evaluation of hazards in food. These standards are also important in facilitating market access and ensuring fair practices in trade—indirectly contributing to development and reducing poverty.

The maximum residue limit (MRL) is the maximum pesticide residue in a specific crop grown with recognized good agricultural practices (GAP) that is expected not to cause harm to human health from dietary consumption. The *Codex* establishes MRLs for pesticides based on scientific risk assessment by the Joint FAO-WHO Meeting on Pesticide Residues (JMPR), a group of independent scientific experts. Countries can use MRLs to develop national regulations.

Compounds already evaluated in the *Codex* process are to be reviewed at least every 15 years. For compounds prioritized by the *Codex* Committee on Pesticide Residues (CCPR), at the request of member countries, an up-to-date toxicological dossier—and crop residue data corresponding to proposed GAP—should be submitted to JMPR by the sponsor, generally the company holding the patent.

JMPR uses the most relevant science available (*5*) but is constrained by the information provided. In general, such data are generated to support the establishment of MRLs and other regulatory decisions by national or regional authorities, such as the U.S. Environmental Protection Agency (EPA), Health Canada, European Food Safety Authority (EFSA), and the Ministry of Health, Labor, and Welfare in Japan.

The information provided should cover oral disposition, including metabolic fate; acute, chronic, and subchronic toxicity; carcinogenicity; reproductive and developmental toxicity; and genotoxicity. Information should be sufficient to assess neurotoxic and immunotoxic potential. This information is used to establish acceptable daily intake (ADI), an estimate of the amount of pesticide residue that can be ingested daily over a lifetime without appreciable health risk.

Where possible, JMPR has paid increasing attention to potential acute effects of pesticide residues. Guidance on the establishment of an acute reference dose (ARfD) was published (*6*). JMPR uses information on mode and mechanism of action for toxic effects to determine human relevance, interpret the dose-response relation, and identify inter- and intraspecies safety and uncertainty factors (*7*, *8*).

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Potential Outcomes for Generic Pesticides

For old compounds no longer supported by their initial producer, a decision needs to be made on whether to prioritize them for dietary risk assessment or to withdraw the previously established MRLs. Removal of MRLs renders crops with residues of the pesticide in question subject to enforcement actions. A procedural solution is needed to replace the compound's original sponsor when their assessment is requested by member countries.

As manufacturers change from the original patent holder to generics companies, the technical specifications of the substance may change—for example, impurity profiles or isomeric composition. The specification

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of the active substance in current use must be provided for JMPR to assess toxicity.

Ideally, JMPR should have access to original, quality-assured reports containing all summary and individual animal toxicity test data. This will not always be possible. Where secondary sources, containing only summary information, are used, these must contain sufficient information to enable study findings to be reconstructed, with adequate information on the response at all dose levels for all key end points. Secondary sources might be reviews by other authoritative bodies, such as EPA or EFSA, or previous assessments by JMPR or WHO's International Programme on Chemical Safety.

As with all substances, whether fully supported by the original commercial sponsor or not, a full search of the peer-reviewed literature will be undertaken. For some compounds no longer supported by the original sponsor, greater reliance will need to be placed on such publications. JMPR will weigh these publications, as with any study report, for their quality and design.

JMPR is not a regulatory body, so it does not prescribe mandatory data requirements. Hence, minor data gaps may be tolerable. JMPR will use its best judgment as to whether gaps are of such a concern that it would not be appropriate to confirm or establish an ADI and/or an ARfD. Where data gaps prohibit confirming or establishing an ADI and/or ARfD, JMPR will provide guidance information that would be useful for further evaluation of the compound. Depending on need, the necessary studies may be commissioned by a member country, manufacturer, research organization, or other party.

Areas where outcomes are likely to differ, depending on whether a comprehensive data package is provided by the original sponsor, include the following:

Establishment of an ARfD. Due to differences in study design, earlier studies may place less emphasis on nonpathological effects than modern studies.

Information on mode of action, the intermediate biochemical and pathological processes leading to an adverse effect. Substances no longer supported by the original sponsor are less likely to have follow-up information on mode of action for cancer or noncancer end points. When irrelevant modes of action are not ignored, risk assessments could become more conservative.

In the absence of mode-of-action information, it is less likely that it will be possible to use chemical-specific considerations in the choice of safety and uncertainty factors. The default judgment is that, on average, humans may be 10 times as sensitive as experimental animals, on a per-body weight basis, and that some human subpopulations may be 10 times as sensitive as the average (*5*). The two factors of 10 can be subdivided into subfactors for differences in how the substance enters and is processed by the body (toxicokinetics) and in toxicological response to the substance (toxicodynamics). Information on intermediate processes underlying mode of action may support substance-specific modification, which would not be possible without knowledge of the mode of action (*5*).

Toxicity of metabolites. Where metabolites formed in plants or livestock contribute to the residue that is consumed, JMPR will seek assurance that there is sufficient information to assess toxicity. It may be that sufficient information is formed in laboratory species that it would have been covered in assessment of the toxicity of the pesticide itself. If specific to treated plants or livestock, additional information on toxicity would normally be required unless structural similarity was sufficient to rely on the toxicity profile of the pesticide itself.

Recent JMPR assessment of dicofol and fenvalerate illustrates these issues. Neither compound was supported by original sponsors, but JMPR was provided with sufficient information to establish ADIs and ARfDs. The original dicofol manufacturer provided original reports of toxicological studies to the sponsoring government, India, where dicofol is used to control mites on tea. The EPA was authorized to permit access to reports of toxicological studies from the original fenvalerate manufacturer. In no case was it necessary to use a safety and uncertainty factor >100 (in 2005, a safety factor of 500 was used with ethoxyquin owing to inadequate information). For both compounds, the ARfD was based on acute effects observed after a single dose. Information provided on the likely mode of action of fenvalerate for microgranulomatous lesions observed in lymph nodes and other tissues provided reassurance that these were of low biological significance to humans (*9*).

Proposals to Update Procedures

In 2013, the CCPR updated one of its fundamental documents dealing with risk analysis principles and the roles of JMPR, CCPR, and CAC to account for new needs of member countries (*10*). Member countries agreed that when the company owning a pesticide's patent is no longer interested in commercialization, a member country may submit to JMPR a dossier that need not necessarily contain raw data generated by the original sponsor. This will allow trade of food containing residues from these compounds, which should be an incentive for generating data for safety assessment and ultimately to discourage use of pesticides not (re)evaluated.

Member countries also agreed that all compounds listed for reevaluation after 15 years could remain on this list for up to 10 years, during which time a member country would need to express interest in supporting the compound. This time frame seems more realistic to allow generation of adequate data without support of the original sponsor. In the absence of member country interest, MRLs should be automatically deleted and the compounds no longer used in food for international trade. Where there is interest in continued availability, a member country should propose that CCPR prioritize the compound for reevaluation and provide the JMPR with adequate data for its evaluation.

The *Codex Alimentarius* process of developing international MRLs, started 50 years ago, is essential but insufficient. Ensuring that pesticides are used properly so as not to violate MRLs requires proper licensing of pesticides, clear instructions on their use, pesticide application education and training, and enforcement of pesticide regulations.

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