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Review of California's Risk-Assessment Process for Pesticides

ISBN
978-0-309-36775-2

80 pages
6 x 9
PAPERBACK (2015)

Committee to Review Californiaâ€™s Risk-Assessment Process for Pesticides; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Research Council

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Review of California's Risk-Assessment Process for PESTICIDES

Committee to Review California's
Risk-Assessment Process for Pesticides

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

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Washington, D.C.
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This project was supported by Agreement 13-C0026 between the National Academy of Sciences and the California Department of Pesticide Regulation. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-36775-2
International Standard Book Number-10: 0-309-36775-1

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Preface

The California Department of Pesticide Regulation (DPR) conducts risk assessments as part of its mission to protect human health and the environment by regulating pesticide sales and use in the state. Premarket evaluation of pesticide products that have been approved by the US Environmental Protection Agency (EPA) is used to determine whether a product can be used safely in California. Risk assessments are also undertaken by DPR during the re-evaluation of registered pesticides or if an important health hazard resulting from exposure to a pesticide is identified. To ensure that DPR's assessments use the best scientific information and current methods, DPR arranged for an independent peer review of the agency's risk-assessment practices. Because the National Research Council has produced several important reports outlining improvements in the practice of risk assessment, DPR asked it to review whether DPR's risk-assessment practices are scientifically and technically credible and to identify ways to improve the agency's efficiency and productivity.

In response to DPR's request, the National Research Council convened the Committee to Review California's Risk-Assessment Process for Pesticides, which prepared this report. The members of the committee were selected for their expertise in toxicology, epidemiology, agronomy, occupational health, exposure assessment, and risk assessment. Appendix A has biographic information on the members.

The committee held public meetings to collect information on DPR's risk-assessment process, to clarify relevant information about EPA's pesticide program, and to get input from stakeholder groups. The committee thanks Sheryl Beauvais, Svetlana Koshlukova, Brian Leahy, Gary Patterson, Andrew Rubin, Randy Segawa, and Marylou Verder-Carlos, of DPR, for their presentations and assistance with providing background information on DPR's risk-assessment practices. The committee also thanks the following for their presentations and other input: William Jordan, EPA; Anne Katten, California Rural Legal Assistance Foundation; and Arthur Lawyer, Technology Sciences Group.

The committee's report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of the independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following for their review of the report: Steven Bradbury, Steven Bradbury and Associates; Robert Brent, Thomas Jefferson University; Thomas Cline, University of California, Berkeley; Richard Jackson, University of California, Los Angeles; Susan Kegley, Pesticide Research Institute; Timothy Pastoor, Syngenta Crop Protection, Inc.; Nu-May Ruby Reed, Davis, CA; Diane Rohlman, University of Iowa; Larry Sheets, Bayer CropScience; and Mae Wu, Natural Resources Defense Council.

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by Deborah Cory-Slechta, University of Rochester, and David Savitz, Brown University. Appointed by the National Research Council, they were responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the author committee and the institution.

The committee is grateful for the assistance of National Research Council staff in preparing the report. It particularly wishes to acknowledge the support of project director Susan Martel, who coordinated the project and contributed to the committee's report. Other staff members who contributed to this effort are Camilla Ables, program officer in the Board on Agriculture and Natural Resources; James Reisa, director of the Board on Environmental Studies and Toxicology; Tamara Dawson, program associate; Norman Grossblatt, senior editor; and Mirsada Karalic-Loncarevic, manager of the Technical Information Center.

Finally, I thank all the members of the committee for their efforts throughout the development of this report.

Marion F. Ehrich, PhD
Chair, Committee to Review California's
Risk-Assessment Process for Pesticides

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Abbreviations

ADI	acceptable daily intake
AEAP	Adverse Effects Advisory Panel
AI	active ingredient
ARB	Air Resources Board
BMD	benchmark dose
CalEPA	California Environmental Protection Agency
CDPH	California Department of Public Health
CSFII	US Department of Agriculture Continuing Survey of Food Intake by Individuals
DFROII	Doctor's First Report of Occupational Illness and Injury
DPR	Department of Pesticide Regulation
EPA	US Environmental Protection Agency
IRIS	EPA's Integrated Risk Information System
MOE	margin of exposure
NHANES	National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRC	National Research Council
OEHHA	Office of Environmental Health Hazard Assessment
PBPK	physiologically based pharmacokinetic
PHED	Pesticide Handler Exposure Database
PISP	Pesticide Illness Surveillance Program
PREC	Pesticide Registration and Evaluation Committee
PUR	Pesticide Use Reporting
RAPWG	Risk Assessment Prioritization Work Group
RCD	risk-characterization document
RfC	reference concentration
RfD	reference dose
TAC	toxic air contaminant
USDA	US Department of Agriculture

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Summary

The California Department of Pesticide Regulation (DPR) conducts human health risk assessments as part of its mission to ensure the protection of workers and public health in the state. The risk assessments identify potential health hazards posed by pesticides, characterize dose–response relationships, and estimate exposure to characterize potential risks to humans. Over the last decade, advances in methods of scientific and technical analysis have led to improvements in the risk-assessment process that have made them more rigorous, transparent, and useful to risk managers. In light of the advances, DPR arranged for an independent peer review of the agency's risk-assessment practices to ensure that they are scientifically and technically credible.

DPR asked the National Research Council to conduct the independent review. In response to the request, the National Research Council convened the Committee to Review California's Risk-Assessment Process for Pesticides to determine whether DPR's processes of hazard identification, exposure assessment, dose–response analysis, and risk characterization are consistent with best practices, such as those outlined in recent National Research Council reports. The committee also was asked to evaluate the methods used for setting priorities among pesticides for risk assessment and to identify possible options for improving efficiency and productivity.

SETTING PRIORITIES AMONG PESTICIDES

Over 300 pesticides are candidates for risk assessment in California because of concerns about their potential adverse health effects. They include new pesticides and state-registered pesticides that are undergoing re-evaluation because a potential health hazard has been identified. A priority-setting process is used by DPR to focus its resources on pesticides that pose the greatest risks to human health. The process involves establishing a list of candidate pesticides for risk assessment; screening and categorizing them into groups of high, medium, and low priority; and identifying and ranking the top 10 candidates for risk assessment. Four advisory panels are involved in the categorization, ranking, and review of the priorities at various stages of the process. Criteria used by the panels to set priorities fall into categories of physical and chemical properties, toxicity data, and potential for exposure. Reports of pesticide-related illnesses are also considered.

The screening process used by DPR to categorize pesticides into high-, medium-, and low-priority groups is practical given the large number of pesticides that DPR must consider. The criteria used to select the top 10 pesticides for risk assessment are reasonable and help to minimize the possibility that humans will incur excess risk during the time required to complete the assessment and make risk-management decisions. Strengths of the process include public consultation on the priority lists and the involvement of scientific review and stakeholder groups in the selection process. Periodic re-evaluation of the high-, medium-, and low-priority lists and annual selection of 10 pesticides for risk assessment are also commendable.

Although the committee generally supports DPR's priority-setting process, it identified several improvements that will help to make the process more transparent and defensible. First,

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better documentation of the evidence used to place pesticides into high, medium, and low categories is needed. Second, a more structured and objective ranking process is needed to ensure that DPR is focusing on the most important compounds. The current processes used to select the top 10 pesticides from the high-priority list of candidates are fairly subjective and depend on the expertise and knowledge of the persons conducting the reviews. Although documents describing the selection of the top candidates are available, the discussions are qualitative and do not explain how consideration of the criteria led to the ultimate ranking of the 10 pesticides. A more formal approach would make the rankings more defensible, ensure that a consistent ranking approach is applied, help outside parties to understand how priorities are established, and provide a baseline description of the methods that would be used if DPR decides to make modifications in the future.

Recommendations:

- *DPR should update its documentation of its priority-setting process to provide more details so that the public can understand the process better. Flow diagrams would be helpful in documenting the steps in the process, identifying the staff and peer-review groups involved in each step, and indicating the opportunities for public input.*
- *DPR should provide more explicit documentation and support for how pesticides are categorized into groups of high, medium, and low priority.*
- *DPR should develop a more objective and structured approach for ranking high-priority pesticides so that others could reasonably reproduce the rankings. One option to consider is the development of a scoring system to weight the different factors. Such a scheme could provide greater transparency in illustrating how the 10 high-priority candidates for risk assessments were selected. If such a scheme were developed, it would be important to have it peer-reviewed before implementation.*

RISK-ASSESSMENT METHODS AND PRACTICES

Problem Formulation

Two of the goals of recent advances in risk assessment were to improve transparency of analyses and judgments and to increase the utility of risk assessment for decision-makers. Important steps in achieving those goals are problem formulation and scoping. The 2009 National Research Council report *Science and Decisions: Advancing Risk Assessment* advocates that those steps be performed in consultation with decision-makers because it is critically important for the people who perform the risk assessment to understand the questions being asked and the decisions to be made by risk managers. Under the statutes within which DPR operates, it might be possible to develop a general catalog of the decisions and the options for making them. Such a catalog would help to ensure that the decisions and options are clearly set forth and that the set of considerations applied to each problem is consistent. Many of the committee's concerns about improving California's risk-assessment process for pesticides would be lessened if there were a description of problem formulation for each assessment, including a conceptual model and analysis plan that outlined the technical details for conducting the assessment. There should continue to be separation between risk assessors and managers with respect to any influence on the outcome of the assessment, but joint planning in the early stages of the process to identify and formulate the needs of risk-managers is likely to improve both the relevance and the efficiency of the assessment.

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Risk-Assessment Methods and Guidance

The committee reviewed guidance documents provided by DPR on how it performs various aspects of its risk assessments. Three of the more recently completed pesticide risk assessments (those of chloropicrin, carbaryl, and methyl iodide) were considered in depth, as were summaries of the 11 most recent risk-characterization documents. Overall, the committee found that DPR's risk-characterization documents are comprehensive and follow established risk-assessment practices but that DPR's risk-assessment guidance documents do not yet reflect recommendations made in recent in National Research Council reports. The bulk of the assessments duplicate much of the work of the US Environmental Protection Agency (EPA). For example, similar critical effects are identified, the same studies are considered, and comparable approaches are used by the two agencies. However, differences between DPR and EPA at multiple stages of the risk assessments, including the ultimate reference values derived, were fairly common. In the more recent cases, DPR's reference values were lower than EPA's. Overall, however, the differences were usually small and almost always within an order of magnitude of each other. The differences are due to reasonable differences in scientific interpretation and judgment and generally fall within the level of uncertainty that is inherent in modern risk assessments. Thus, the committee questions whether the extensive effort needed to conduct a comprehensive risk assessment independently of EPA is justified in light of DPR's resources. In the committee's judgment, there are considerable benefits to harmonizing approaches among DPR, EPA, and other relevant agencies with respect to hazard identification and dose–response analysis for most pesticides.

Under DPR's current paradigm, it appears to take several years for a risk assessment to be made final. If DPR could rely more on EPA's evaluations for hazard identification and dose–response assessment, more of its resources could be directed to exposure assessment. Exposure assessments performed by DPR provide the greatest benefit when they introduce state-specific considerations into the risk-assessment process, so the collection of more California-specific information would be valuable.

Recommendations:

- *DPR should review the legislative mandates under which it works to determine whether an independent and comprehensive evaluation of pesticides is required in every case in which a risk assessment is performed. If no new and compelling toxicology data have been generated since an EPA assessment was conducted and if there is no reason to believe that the EPA assessment is seriously flawed, DPR could rely on EPA's assessment to identify the critical studies for hazard identification, interpretation of the dose–response data, and derivation of reference values. That would permit DPR to focus its efforts on California-specific issues, to tailor its risk assessments to its needs, to complete them more quickly, and to complete more of them in a timely fashion.*
- *When an independent assessment is warranted, DPR should incorporate problem formulation and other relevant elements recommended in the 2009 National Research Council report* Science and Decisions: Advancing Risk Assessment *into its risk-assessment process. An important consideration is that risk managers should be consulted in the problem-formulation stage so that a risk assessment can be designed to address the decisions that need to be made by managers and other stakeholders. Consideration should be given to whether a general set of problems and risk-management options could be formulated to use as a starting point in problem formulation.*
- *DPR should update its risk-assessment guidance documents regularly and perhaps develop additional reference materials to reflect the most current risk-assessment practices. DPR should provide better documentation of the guidance to be followed, ensure that the bases of selection and application of default assumptions are explicitly set forth, and that the guidelines*

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are followed in practice. The guidance should draw from the work of EPA, the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment, and other relevant agencies. That will help to standardize and streamline reviews and evaluation approaches and will promote consistency among the assessment teams and contributors. Key subjects for which new guidance should be considered include incorporation of human variation in susceptibility to cancer, risks to susceptible subpopulations, and the types of evidence and justification necessary to permit departure from defaults.

California Data to Inform Priority-Setting and Risk Assessment

DPR supplements its exposure assessments with California-specific information, which the committee judges to be the most valuable contribution to DPR's risk-assessment process. California routinely collects data on agricultural and other pesticide uses, air concentrations of some pesticides, residue data, and reports of human pesticide-related illnesses. California's Pesticide Use Reporting (PUR) program is recognized as one of the most comprehensive in the nation. The program requires that pesticide use in the state be reported monthly, but this requirement applies only to agricultural uses, not to home-and-garden use or most industrial and institutional uses. The California Air Resources Board collects measurements of ambient concentrations of pesticides that are deemed toxic air contaminants.

Another important program is the Pesticide Illness Surveillance Program, which collects information on pesticide-related illnesses. The program is probably capturing only a moderate percentage of cases, because the submission of a case report depends on a person's being seen by a physician, a physician's recognizing that the illness is pesticide-related, and the physician's taking the action necessary to report the case. However, case reports are a useful indicator of potential hazard and are used by DPR in setting priorities among pesticides for risk assessment.

Recommendations:

- *Consideration should be given to expanding the PUR requirements to include all licensed pesticide appliers; these would include those who perform applications for nonagricultural purposes in homes, institutions, and industries if licensed appliers are not already required to do so. The resulting data would help to fill gaps in information about exposure in these types of pesticide uses.*
- *If resources allow, PUR data should be reviewed in relation to air-monitoring data and pesticide-illness surveillance data to determine whether any patterns are evident and to judge the accuracy of exposure assumptions or models.*
- *Consideration should be given to improving the reporting of cases of pesticide-related illness, for example, by improving the training of physicians, expanding the means by which cases can be reported, searching electronic health records, and possibly expanding the use of biomarkers.*

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Introduction

California's Department of Pesticide Regulation (DPR), a department of the California Environmental Protection Agency (CalEPA), is responsible for ensuring the protection of workers, public health, and the environment from effects associated with pesticide use in the state. Emphasis on pesticide risk assessment in California stems from the 1984 Birth Defect Prevention Act. The law prohibited DPR from registering new pesticides without a full complement of health studies and mandated that registrants of older pesticides (those registered before 1984) update their health-effects data to current standards. The law required DPR to identify adverse effects and to determine their importance in making registration decisions. Thus, risk assessment plays a critical role in DPR's evaluation of potential health hazards related to exposure to pesticides and is the basis of new regulations and other use restrictions.

The US Environmental Protection Agency (EPA) conducts comprehensive reviews of active ingredients in new pesticides before federal registration, and DPR allows federally approved active ingredients to be registered in California on a conditional or interim basis without a risk assessment provided that all data required by EPA have been submitted to the state. California may also require registrants to submit additional data to support registration. Priorities are then set for risk assessment of newly registered active ingredients and state-registered pesticides undergoing re-evaluation by DPR. DPR performs its own risk assessments so that California-specific concerns are addressed, including state-specific cropping patterns, climatic and cultural conditions, and worker practices. In addition, because residential areas are much closer to agricultural boundaries in California than in many other states, more emphasis is placed on risks posed by off-site movement of pesticides (Sokolow 2003; DPR 2011).

After registration, DPR has a process for continuous evaluation and re-evaluation to detect potential problems. California has one of the most extensive residue-monitoring programs in the nation; data are collected on residues from preharvest crops, postharvest of raw produce, postharvest commodities, and fresh produce in the marketplace. Exposure monitoring studies are conducted to collect data on pesticide exposure patterns and to assess the effectiveness of existing controls. DPR also has projects for monitoring air quality, groundwater, and surface water under field conditions specific to California. Potential health concerns are identified through investigations into pesticide illnesses and incidents and from mandatory registrant reports on adverse effects of registered products (DPR 2011). Data from those and other sources may trigger the need for a re-evaluation of a registered pesticide. Priorities for risk assessment of registered pesticides and new pesticides are set according to which ones pose the greatest risk to human health.

DPR's risk assessment consists of five steps: hazard identification, dose–response assessment, exposure assessment, risk characterization, and risk appraisal. The department's Medical Toxicology Branch conducts the hazard identification, and the Work Health and Safety Branch conducts the exposure assessment. DPR uses those evaluations to prepare a risk-characterization document for each pesticide. The documents undergo peer review that involves scientists in

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DPR, CalEPA's Office of Environmental Health Hazard Assessment, and EPA and other relevant experts. Some pesticides are also regulated under the Toxic Air Contaminant Act if their active ingredients could pose a health threat as air pollutants. The Toxic Air Contaminant Program focuses on the evaluation and control of pesticides in ambient community air (DPR 2011).

THE COMMITTEE'S TASK AND APPROACH

DPR arranged for an independent peer review of its human health risk-assessment practices to ensure that they are scientifically and technically credible and to identify ways to improve efficiency and productivity in the process so that risk assessments could be completed more quickly. The National Research Council has published guidance on various aspects of human health risk assessments that are highly relevant to this endeavor (NRC 2009, 2011, 2014). Thus, DPR asked the National Research Council to convene a committee of experts to review its risk-assessment practices. The charge to the committee is presented in Box 1-1.

To address its task, the committee held three meetings. Public data-gathering sessions were held at the first two meetings; the committee met with representatives of DPR, EPA's Office of Pesticide Programs, a worker-advocacy group, and pesticide registrants. Open-microphone sessions were held in both meetings to hear the views of other interested stakeholders. As specified in its charge, the committee focused on determining whether DPR's risk assessments are being performed in a scientifically credible manner. The committee reviewed guidance documents provided by DPR on how it sets priorities for risk assessments and how it conducts its exposure assessments and risk assessments. It also reviewed three pesticide-specific risk assessments for the purpose of understanding the procedures and practices of DPR, but it did not evaluate the adequacy of these individual assessments. A list of the documents that the committee considered is presented in Appendix B.

ORGANIZATION OF THIS REPORT

The committee's review of DPR's risk-assessment practices is presented in three chapters. Chapter 2 reviews how DPR sets priorities among active ingredients for risk assessment. Chapter 3 evaluates DPR's risk-assessment process in the context of best practices for risk assessment outlined in several recent National Research Council reports. Chapter 4 focuses on the value of collecting and using California-specific use and exposure data to address the needs of the state.

BOX 1-1 Statement of Task

An ad hoc committee will conduct an independent scientific and technical evaluation of the CalEPA's risk-assessment process for pesticides. The committee will examine documents provided by DPR on the processes it uses for hazard identification, exposure assessment, dose–response analysis, and risk characterization. Consideration will be given to whether the methods and approaches are consistent with best practices, such as those outlined in recent NRC risk-assessment reports. The committee will also evaluate the methods used for prioritizing chemicals for assessment, and the overall process that DPR uses to complete risk assessments to identify possible options for improving process efficiency and productivity.

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2

Setting Priorities Among Pesticides for Risk Assessment

The US Environmental Protection Agency (EPA) regulates all pesticides that are sold and distributed in the United States. After comprehensive scientific analyses and other assessments are performed and EPA grants a registration, registrants are required to comply with individual registration requirements imposed by a state to register the pesticide in the state. In California, all new pesticide active ingredients (AIs) are candidates for risk assessment, as are those already approved and undergoing re-evaluation because a potential health hazard has been identified. Under California statutory requirements, the Department of Pesticide Regulation (DPR) focuses its resources on the AIs that pose the greatest risks to human health. The AIs of greatest concern are identified through a priority-setting process, which was outlined by DPR in four documents provided to the committee: a description of the priority-setting process (DPR 2004), a master list of AIs under consideration (DPR 2011), and two examples of how candidates for risk assessment are selected from the master list (DPR 2007; Schreider 2014). The sections below summarize DPR's priority-setting process and then the committee's evaluation of the examples that it reviewed.

CALIFORNIA'S PRIORITY-SETTING PROCESS

The four documents provided by DPR on its priority-setting activities were informative in getting a general sense of the overall process, but some details had to be inferred, and inconsistencies were found among the documents. This section summarizes the committee's understanding of DPR's process.

DPR's priorities for conducting risk assessments are focused on the AIs that pose the greatest risks to human health. The toxicology database required for federal registration under the Federal Insecticide, Fungicide, and Rodenticide Act is the primary source of toxicity information. Other reliable information is also considered in both priority-setting and risk assessment. If exposure data on AIs are not available at the priority-setting stage, estimates are based on the best available information. Box 2-1 provides a description of the candidate selection and priority-setting process. During the process, DPR has multiple opportunities to interact with staff of other California agencies, stakeholders, the public, and a scientific review panel.

Both new pesticides and state-registered pesticides are candidates for risk assessments. Re-evaluation of registered pesticides is usually triggered by evidence of a potential human health hazard, such as from worker incidence reports or cases of environmental contamination, but may also be triggered by discovery that data on which DPR relied to register a product are incomplete, outdated, or based on other compelling information that suggests an adverse risk to people or the environment. DPR produces semiannual reports that describe the pesticides undergoing re-evaluation and ones that were considered but were judged not to be in need of re-evaluation (DPR 2011).

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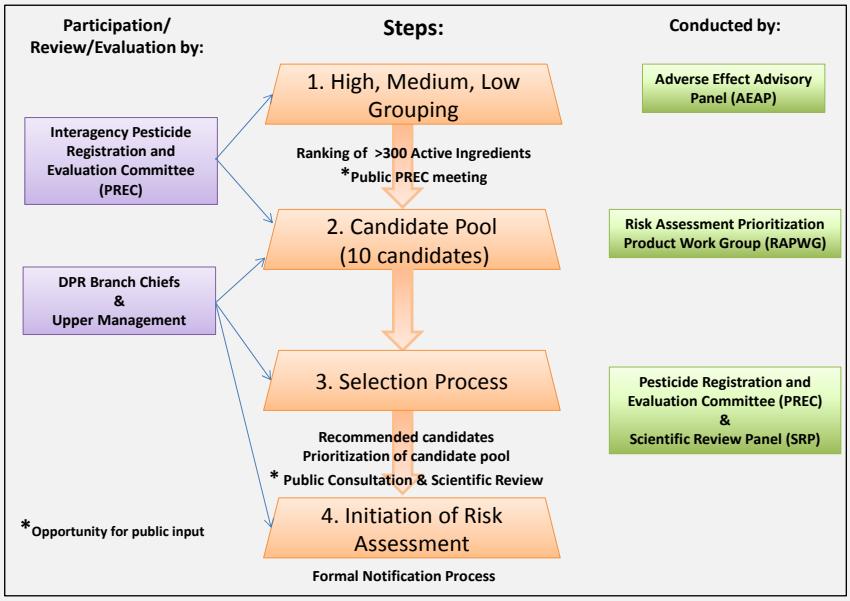
Review of California's Risk-Assessment Process for Pesticides

BOX 2-1 DPR's Candidate Selection and Priority-Setting Process for Pesticides



1. High, Medium, Low Grouping: AIs are placed into groups of high, medium, or low priority for risk assessment by AEAP. PREC reviews the groupings.
2. Candidate Pool: RAPWG selects and ranks a group of 10 candidates for risk-assessment initiation.
3. Selection Process:
   - 3.1. Recommended candidates: On the basis of staffing and other resources, DPR determines how many risk assessments can be initiated in the coming year.
   - 3.2. Prioritization of candidate pool: Senior DPR scientists and branch chiefs make recommendations to upper management on the specific AIs that should enter the risk-assessment process.
   - 3.3. Public consultation and scientific review: The recommendations are posted on DPR's website, made available to interested parties, and reviewed by the PREC and SRP.
4. Initiation of Risk Assessment:
   - 4.1. After evaluating comments, DPR decides which AIs will enter the risk-assessment process.
   - 4.2. Risk assessments are initiated through a formal notification process.

Source: Prepared by the committee on the basis of the processes outlined by DPR (2004, 2011) and Schreider (2014).

AIs are grouped into high-, medium-, and low-priority categories by an Adverse Effects Advisory Panel[1] (AEAP) according to the criteria described in Box 2-2. All criteria are weighted equally, and a qualitative process is used to categorize AIs. AEAP meets periodically to update the groupings. Updates may include the addition of new AIs, the removal of AIs when registrations are canceled or when a risk assessment has been completed, and changes in categorizations

[1]AEAP is composed of senior scientists in three DPR branches (Medical Toxicology, Worker Health and Safety, and Environmental Monitoring), the California Environmental Protection Agency Office of Environmental Health Hazard Assessment, and EPA.

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BOX 2-2 Summary of Criteria Used by DPR to Set Priorities

The criteria used to set priorities among AIs for risk assessment and to identify the ones that could pose the greatest health risks can be divided into three categories of risk drivers: physical and chemical properties, toxicity, and exposure. Other factors that may affect priorities include eradication programs for new pests and regulatory actions by other state or federal agencies. DPR (2004) provides a more comprehensive description.

- Physical and chemical properties—such as vapor pressure, half-life, and solubility—are used to understand how and to what degree an AI might be released into the environment and be available for human exposure. Potential for bioaccumulation or bioconcentration is also considered.
- Toxicity considerations include the magnitude or severity of effects, the number of reported effects, the number of species affected, potency, dose–response information, and mechanism of action.
- Exposure considerations include types of potential exposure, use patterns, type of formulation, methods of application, and projected changes in use. Case reports from the Pesticide Illness Surveillance Program are also used as indicators of exposure potential.

Source: DPR (2004).

when new data on AIs become available. AEAP's conclusions are reviewed by DPR's Pesticide Registration and Evaluation Committee[2] (PREC). A subset of 10 high-priority candidates for risk assessment are selected from the master list and ranked by the Risk Assessment Prioritization Work Group[3] (RAPWG) annually. Focusing risk-assessment efforts on the top 10 candidates helps to minimize the possibility of investing assessment and management efforts on lower-risk compounds. Criteria described in Box 2-2 and scientific expertise in and detailed knowledge of pesticides are used to select 10 AIs (drawn primarily from the high-priority category). After the recommendations are approved by DPR management, a 45-day comment period is initiated and an announcement posted to DPR's website. The announcement is also sent to interested parties, including a Scientific Review Panel (SRP),[4] and is reviewed at a meeting of the PREC. After evaluating comments, DPR determines which AIs will enter the risk-assessment process. Risk assessments are initiated through a formal notification process.

COMMITTEE'S EVALUATION

The 2011 master list of candidates for risk assessment contains 323 AIs, of which 82 are categorized as of high priority, 143 moderate priority, and 98 low priority (DPR 2011). The criteria in Box 2-2 include a reasonable set of risk drivers for setting priorities, but the documentation

[2]PREC includes representatives of California's Departments of Public Health, Food and Agriculture, Industrial Relations, Resources Recycling and Recovery, and Fish and Game; the Structural Pest Control Board; the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment, State Water Resources Control Board, Air Resources Board, and Toxic Substances Control Department; the University of California; EPA, Region 9; the US Department of Agriculture; and the California Agricultural Commissioners and Sealers Association.

[3]RAPWG is composed of two DPR senior scientists in the Medical Toxicology Branch, two senior scientists in the Worker Health and Safety Branch, a senior scientist in the Environmental Monitoring Branch, and one representative each of the Office of Environmental Health Hazard Assessment and the Air Resources Board.

[4]A review panel of the Toxic Air Contaminants program, consisting of scientists in the University of California system.

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supporting inclusion in the master list presents minimal information on studies that indicate possible adverse health effects. No details about the studies are provided, such as the specific health end point of concern, concentrations, test species, or route of exposure. The AIs are listed in alphabetic order in each category, so the master list reflects only a broad screening assessment of the AIs. The committee supports the broad categories used in DPR's screening process but found that better documentation of the information used for making the categorizations is needed.

Examples of how 10 high-priority AIs were selected for risk assessment in 2007 and 2014 were reviewed. Both documents provide summaries of the meetings and activities of the RAPWG and the PREC that led to the selections. The process is somewhat subjective, relying on the expertise of the RAPWG members to identify the AIs of greatest concern, which are later reviewed by the PREC. The 2007 document provided the more substantive description of how the risk-assessment priority list was generated, describing the types of data considered by the RAPWG and the rationale for selection. The 2014 document provided only a brief description of pesticide uses and potential health effects and no clear basis of selection. Neither document provided a clear demonstration of how rankings were based on the evaluation criteria or an apparent way to reproduce DPR's top-10 rankings. Furthermore, no information about why the remaining 70 or so high-priority AIs were not considered and selected is provided. Thus, there was no real *ranking* of AIs that would allow selection of the AIs that posed the highest risk.

FINDINGS AND RECOMMENDATIONS

DPR has a priority-setting process that focuses on identifying the AIs that potentially pose the greatest human health risks. The screening process used to categorize AIs into high-, medium-, and low-priority groups is practical given the large number of AIs that DPR must consider. The criteria used to select the top 10 AIs for risk assessment are reasonable and help to minimize the possibility that humans will incur excess risk during the time required to complete the assessment and make risk-management decisions. Strengths of the process include public consultation on the priority list and the involvement of scientific review and stakeholder groups (the AEAP, the RAPWG, the PREC, and the SRP) in the selection process. Periodic re-evaluation of the high-, medium-, and low-priority lists and the annual selection of the top 10 chemicals are also commendable.

Although the committee generally supports DPR's priority-setting process, it identified several improvements that would help to make the process more transparent and defensible. First, better documentation of the evidence used to place AIs into high-, medium-, and low-priority categories is needed. Second, a more structured and objective ranking process would help to ensure that DPR is focusing on the most important AIs. The current processes used to select the top 10 AIs are fairly subjective and depend on the expertise and knowledge of the RAPWG members. Although documents describing the selection of the top candidates are available, the discussions are qualitative and do not explain how consideration of the criteria led to the ultimate ranking of the 10 candidates. A more formal approach to priority-setting would make the rankings more defensible, ensure that a consistent ranking approach is applied, help outside parties to understand how priorities are established, and provide a baseline description of the methods in case DPR decides to make modifications in the future.

Recommendations:

- *DPR should update its 2004 documentation of its priority-setting process to provide more details so that the public can understand the process better. Flow diagrams would be helpful in documenting the steps in the process, identifying the staff and peer-review groups involved in each step, and indicating the opportunities for public input.*

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- *DPR should provide more explicit documentation and support for how AIs are categorized into groups of high, medium, and low priority.*
- *DPR should develop a more objective and structured approach for ranking high-priority AIs on the basis of the criteria presented in Box 2-2 so that others could reasonably reproduce the rankings. One option to consider is the development of a scoring system to weight the different factors. Such a scheme could provide greater transparency in illustrating how the 10 high-priority candidates for risk assessments were selected. If such a scheme were developed, it would be important to have it peer-reviewed before implementation.*
- *DPR should continue to use California-specific data, such as information from the Pesticide Use Reporting program and the Pesticide Illness Surveillance Program, and perhaps collect additional data to help in setting priorities. (See Chapter 4 for recommendations on improving the collection of California-specific data.)*
- *For each document that sets risk-assessment priorities, DPR should disclose the names and affiliations of the members of the review group (the AEAP, the PREC, the RAPWG, and the SRP) involved in priority-setting to help to increase transparency in the review process.*

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3

Risk-Assessment Practices for Pesticides

The California Department of Pesticide Regulation (DPR) conducts risk assessments as part of its mission to protect human health and the environment by regulating pesticide sales and use. Premarket evaluation of pesticide products that have been approved by the US Environmental Protection Agency (EPA) is used to determine whether a product can be used safely in California. The evaluation is based on EPA standards for registration and studies required by state statutes. The state may register a pesticide product without further assessment, implement restrictions on the use of the product that are more stringent than federal standards, or even deny registration. The premarket evaluation sometimes identifies the need for a more comprehensive risk assessment to support decisions about registering a product in California. Risk assessments are also undertaken by DPR during the re-evaluation of a registered pesticide and if a substantial health hazard resulting from exposure to a pesticide is identified (DPR 2011).

Risk assessments identify potential health hazards posed by active ingredients (AIs), characterize dose–response relationships, and evaluate exposure data to characterize potential risks to agricultural workers and the public. Over the last decade, advances in science and technical analysis have led to improvements in the risk-assessment process that make assessments more rigorous, transparent, and useful to risk managers. This chapter first reviews National Research Council reports that have made key recommendations for improving the practice of risk assessment; specific aspects of DPR's assessments are evaluated in the context of those recommendations. DPR's risk-assessment practices are then reviewed more generally to determine whether they reflect best practices and are optimized for the needs of DPR's risk managers.

BEST PRACTICES IN RISK ASSESSMENT

Lessons from the Silver Book

In 2009, a National Research Council committee issued an influential report, *Science and Decisions: Advancing Risk Assessment* (the "Silver Book"), which was developed in response to a request from EPA. The report offers substantial guidance on improving the *scientific status* of risk assessments and on increasing their *utility for decision-making*. A number of EPA efforts to implement the recommendations found in the Silver Book are under way (EPA 2014), and DPR has asked the present committee to offer guidance on some of the ways in which those recommendations might be used to enhance its program.

The Silver Book reaffirms most of the risk-assessment principles and concepts first elucidated in the National Research Council's 1983 report *Risk Assessment in the Federal Government: Managing the Process* (the "Red Book"): the framework within which risk assessments are to be conducted, the need for inference assumptions (defaults) when data and basic knowledge are lacking, the importance of guidelines that specify the types of scientific evidence and default assumptions that will be used in the conduct of risk assessments, and the important distinctions between risk assessment and risk management. The Silver Book builds on those principles and

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concepts to offer detailed guidance on scientific improvements in risk assessments, some of which can be implemented in the near term and some of which will require substantial study before they can be implemented. The Silver Book also focuses on improving the usefulness of risk assessments.

Improvements in Risk-Assessment Guidelines

Risk-assessment guidelines typically set forth and explain the types of scientific evidence to be relied on in assessing risk and offer guidance on how the evidence is to be collected, organized, and evaluated. Guidelines are necessary to justify and make explicit the specific assumptions that will be used to deal with uncertainties and data gaps, the various forms of extrapolation beyond the data needed to complete risk assessments, and how such issues as population and life-stage variability are to be handled. DPR provided the committee with the guidance documents that it has developed (see Appendix B) and indicated that its guidance on uncertainty factors and calculation of reference values (DPR 2011) is undergoing revision.

Extrapolation models and uncertainty factors, typically referred to as default assumptions, are derived on the basis of both scientific and policy considerations. The Silver Book makes a distinction between explicit defaults and "missing defaults" (implicit assumptions that have become ingrained in risk-assessment practice), and it recommends more explicit treatment of the missing defaults. The Red Book (NRC 1983) and later National Research Council risk-assessment publications, including the Silver Book, have emphasized that the selection of defaults for risk assessment involves policy choices that are of a different kind from those involved in risk management. Thus, the selection of default assumptions is based, to the extent possible, on current scientific understanding; in the absence of complete understanding, a "science-policy" choice is introduced to select the assumptions to be routinely used. The guideline-development process should be explicit with respect to the selections.

Two other principles related to the selection of defaults might be addressed in guidelines (see Chapter 6 of the Silver Book):

- The specification of defaults to be used in risk assessments ensures consistency among assessments and minimizes opportunities for inappropriate manipulation of risk assessments to achieve desired risk-management outcomes.
- Guidelines typically allow departures from default assumptions if compelling scientific data show the inapplicability, in specific cases, of a standard default. In such cases, the data are used rather than the standard defaults. Departures in specific cases should be scientifically justified.

DPR assessments often refer to "weight-of-evidence" (WOE) analyses as the basis of selecting specific uncertainty factors (from a variety of possible factors), but in many cases it is not obvious how the analyses led to the selection of the uncertainty factors. DPR's guidance on default uncertainty factors (DPR 2011) is relatively brief and consists mostly of tables that list default values. Current efforts by DPR to revise its guidelines present an opportunity to provide better justification for default assumptions and more explicit guidance on the factors to be considered in selecting uncertainty factors and extrapolation models. That will help to ensure consistency between risk assessments and provide greater transparency.

There have been occasions in which DPR has departed from its usual defaults, sometimes to use science-based data that have become available in specific cases or for other less clear reasons. The committee recommends that DPR not only elucidate more clearly the bases of its defaults but clarify the criteria to be used for departures from the usual defaults. There is a great risk that without such departure criteria the risk-assessment process may appear to be arbitrary and to be driven by risk-management objectives. Other technical refinements in risk-assessment guidelines are recommended in Appendix C.

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Improving the Utility of Risk Assessment

The Silver Book's recommendations for improving the usefulness of risk assessment for decision-making might be the most important for enhancing DPR's program because many of the recommendations depend on the uses to which risk assessments will be put. Chapter 8 of the Silver Book is devoted to the subject of risk assessment and decision-making and sets out a framework that maximizes the utility of risk assessments (see Figure 3-1 of the present report). The framework encompasses three phases: Phase I involves problem formulation and scoping, Phase II encompasses planning and conduct of risk assessment, and Phase III involves risk management. EPA efforts to adopt the the Silver Book's recommendations offer useful examples and practical guidance (see EPA 2014).

Phase I: Problem Formulation and Scoping

Phase I places emphasis on "problem formulation and the simultaneous (and recursive) identification of risk-management options and identification of the types of technical analyses, including risk assessments, that will be necessary to evaluate and discriminate among the options" (NRC 2009, p. 247). Developing the problem formulation with input from risk managers would allow risk-assessment results to be better understood in the proper framework for risk management. The numbers and types of decisions in the case of DPR are smaller and less variable than those of EPA. The decision types could be formulated as the various problems that DPR is asked to solve, and risk-management options (interventions) to address the problems can be identified (see example questions posed in the box under Phase I of Figure 3-1). Under the statutes under which DPR operates, it might be possible to develop a general catalog of the decisions and options that is generally understood by DPR staff and stakeholders. Such a catalog would help to ensure that the decisions to be made and the options for addressing them are clearly set forth and that a consistent set of considerations is applied to each problem to be addressed. The results of the problem-formulation and scoping process are two products: "a conceptual model that explicitly identifies the stressors, sources, receptors, exposure pathways, and potential adverse human health effects that the risk assessment will evaluate and an analysis plan (or work plan) that outlines the analytic and interpretive approaches to be used in the risk assessment" (NRC 2009, p. 77). They are used in Phase II for planning risk assessments to discriminate between options. Unusual decision-making circumstances that are not covered in the general cases might arise, and they might require new planning, scoping, and problem formulation, but having a general catalog of decisions and options as a starting point could greatly increase program efficiency and transparency.

Phase II: Planning and Conduct of Risk Assessment

Phase II sets the stage for deciding what information and technical analyses are required to provide the information necessary to address the specified problems. A conceptual model and an analysis plan (or work plan) are used to guide the process. Typically, the risk assessment to be undertaken is focused first on an existing situation and then on the effects of the various possible interventions on the existing risks.[1,2] Risk reductions achieved with various risk-management options are thus the key results of Phase II of the risk-assessment process. The framework for risk assessment presented as Stage 2 in Figure 3-1 is identical with the Red Book framework

[1]If an existing situation is seen to pose no important risks, no further analysis or action is necessary.
[2]Interventions typically affect human exposures, not other elements of the risk-assessment process.

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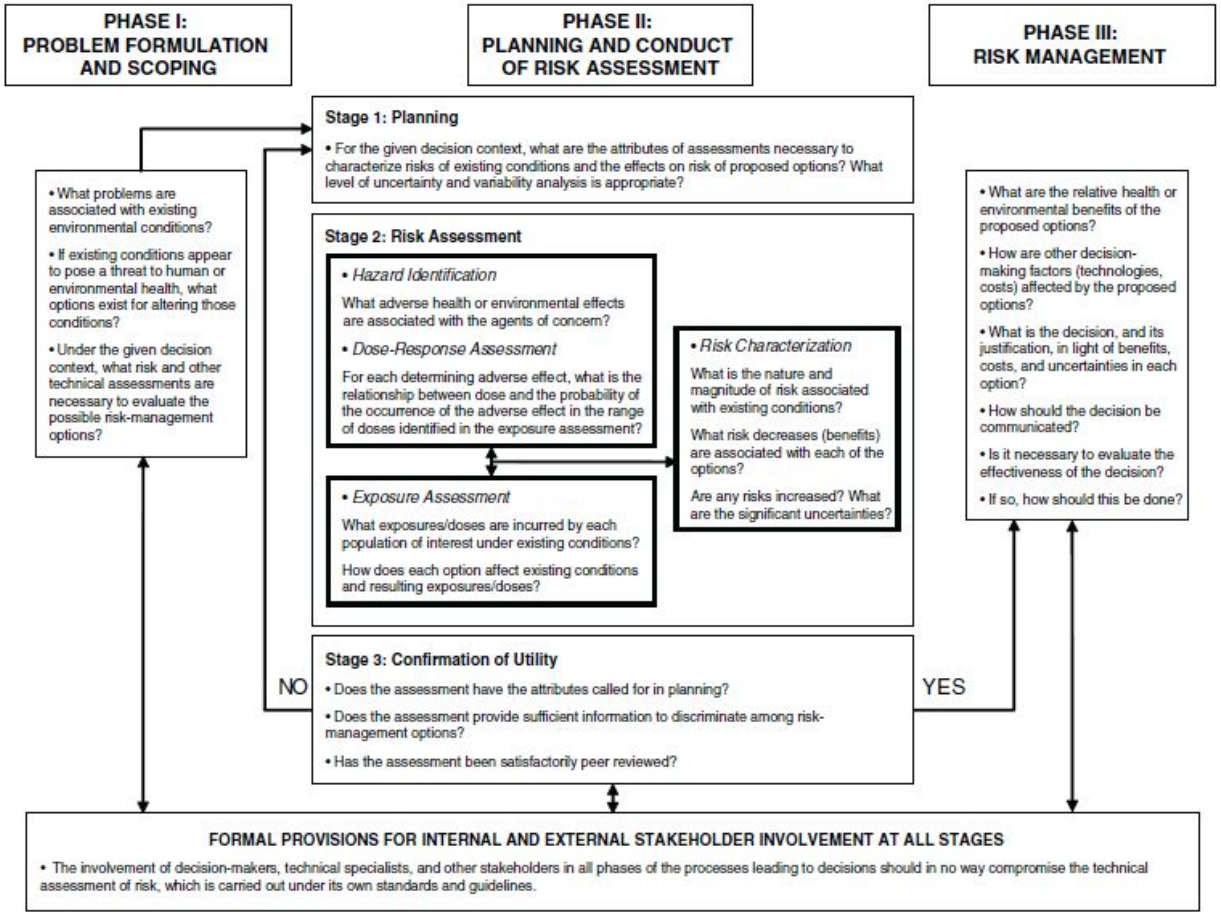

FIGURE 3-1 A framework for risk-based decision-making that maximizes the utility of risk assessment. Source: NRC (2009, p. 11).

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(NRC 1983), and the same "rules" apply to its implementation (it is performed under specific risk-assessment guidelines and is free from interference by risk managers). Analyzing risk reductions associated with various risk-management options is solely a risk-assessment activity. And it is important that it is designed to provide risk managers with the information that they need to make good decisions. The latter is not possible without the type of planning called for in Phase II.

The committee emphasizes that the involvement of risk managers and other stakeholders in Phase II planning is not an inappropriate introduction of risk managers into the risk-assessment process. The involvement of risk managers should be focused on what needs to be evaluated to support good decisions, not on how the evaluation is to be done or what the outcomes should be.

Two other aspects of Phase II will be important for DPR to consider. First, risk assessments can be performed at various levels of technical sophistication, ranging from relatively simple "screening-level" assessments involving minimal data and modeling to highly detailed probabilistic assessments. Not all problems require the same level of risk assessment, and the first step of Phase II involves specifying the level of analysis appropriate for the problem under evaluation. Risk assessment is not an end in itself; its sole use is to support decision-making, so the assessment should always be "fit for purpose".

Second, an important element of Phase II involves a check of the risk assessment to ensure that it has produced the information necessary to address the decision at hand (see Stage 3 in Figure 3-1). This check is performed before the assessment is moved into Phase III, the risk-management process.

Phase III: Risk Management

Risk assessment provides the critical information for decision-making. There may be circumstances in which other types of technical information (such as the relative effectiveness of various pesticides for plant protection and benefit–cost considerations) are also required for decisions (see box under Phase III in Figure 3-1), but health protection is of overriding importance. Thus, decision documents should be clear about how the risk-assessment results and the uncertainties associated with them are used to make the ultimate decision. The risk-management process must be completely transparent. Communication of risk decisions also needs to be clear and appropriate for the intended audience of stakeholders. Decisions do not automatically flow from the technical analyses, especially inasmuch as all such analyses contain uncertainties. Responsible risk management requires clear exposition of the path from risk assessment and other relevant technical analysis to the ultimate decision. The committee found that DPR's risk-appraisal step is a highly valuable aid to the management process in this regard.

The committee emphasizes that risk managers are not to alter risk-assessment results. If the managers find the results not useful in some way, it is an indication that the important Phase I process of planning and scoping has failed. The proper course, if such circumstances arise, is to return to Phase I planning and the development of a more useful risk assessment.

Stakeholder Involvement

The Silver Book emphasizes the importance of stakeholder involvement in all phases of the decision framework (see box at the bottom of Figure 3-1). The involvement of stakeholders—including technical specialists, risk managers, and affected parties—is important to ensure the efficiency and relevance of the analyses undertaken to support decisions. The transparency of the entire process (all three phases) is essential, and DPR should take steps to ensure that there are no exceptions to this requirement. The agency might consider developing explicit guidance on how stakeholders can be involved (for example, see Chapter 3 of EPA 2014).

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Review of California's Risk-Assessment Process for Pesticides

Scientific Improvements in Risk Assessment—Near Term

Two sets of recommendations in the Silver Book appear already to have an important presence in DPR's risk-assessment practices. One concerns treatment of uncertainty and variability, and the second concerns the use of defaults. The committee's evaluation of DPR's current practices in those issues is discussed later. Here, the committee emphasizes additional features of the treatment of uncertainty and variability that might enhance DPR's program further.

The Silver Book emphasizes the need to ensure that the level of uncertainty analysis is appropriate to the problem under evaluation. Uncertainty can be discussed simply at a purely qualitative level or, at the other extreme, probabilistically. It is a principle that analysis of risk and uncertainty should be carried out at a level of detail and sophistication appropriate to the problem at hand, and the appropriate level should be specified before the analysis is undertaken. (See Chapter 4 of the Silver Book for guidance on the "design" of risk assessments.) One goal of such recommendations is to avoid wasting time and resources on unnecessary technical analysis. It is not clear that DPR's current approach to uncertainly analysis conforms to those principles.

The Silver Book makes a number of recommendations for improving the selection and use of defaults, which DPR should consider in updating its guidance documents. For example, the agency should begin developing explicit defaults to use in place of missing defaults, such as defaults for human variation in susceptibility to cancer and for risks to susceptible subpopulations (during early life for other stages). Guidance documents should provide clear rationales for the basis of all the defaults. The Silver Book also advocates that standards and criteria for departing from defaults be developed. Such a system would include an "evidentiary standard" for considering alternative assumptions in relation to defaults and establishing criteria for gauging whether an alternative model has met the evidentiary standard.

Scientific Improvements in Risk Assessment—Long Term

Chapter 5 of the Silver Book ("Toward a Unified Approach to Dose–Response Assessment") recommends a move toward quantitative measures of risk for all end points. It advocates that the approach include (NRC 2009, p. 9)

> use of a spectrum of data from human, animal, mechanistic, and other relevant studies; a probabilistic characterization of risk; explicit consideration of human heterogeneity (including age, sex, and health status) for both cancer and noncancer end points; characterization (through distributions to the extent possible) of the most important uncertainties for cancer and noncancer end points; evaluation of background exposure and susceptibility; use of probabilistic distributions instead of uncertainty factors when possible; and characterization of sensitive populations.

Those are far-reaching recommendations, and their general implementation will require many years of study and research. Relevant efforts are under way in EPA and the California Environmental Protection Agency (CalEPA) Office of Environmental Health Hazard Assessment (OEHHA).

The current approach to risk assessment for all noncancer end points involves the establishment of toxicity reference doses (RfDs), reference concentrations (RfCs), or their equivalents. Those values are *not* expressions of risk, except in a qualitative sense (exposures at or below the values are likely to pose little risk to health). Even more problematic is the fact that their use in decision-making provides no guidance on the probabilities of adverse effects at higher or lower doses or concentrations. In contrast, cancer risks are generally expressed as probabilities, so it is possible to quantify risks and how risk declines as exposures decline (in association with various possible risk-management interventions). Given a robust database on which to base the quantitative model, this type of risk

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information is highly useful for decision-making. The use of RfDs or RfCs is not helpful in that respect, because they are "bright lines" and offer little flexibility for decision-making.[3] Implementing the approach set forth in the Silver Book will lead to quantitative expressions of risk for all toxic end points, whether toxicity occurs by a threshold or nonthreshold mode of action, although the requirement for quantitative expressions of risk is decided during Phase II planning (specifying the level of analysis appropriate for the problem under evaluation).

DPR develops margin-of-exposure (MOE) estimates in its risk-characterization documents for noncancer end points. The MOE is the magnitude by which a toxicity value (such as a no-observed-effect level) exceeds the estimated exposure dose. The larger the MOE, the smaller the estimated risk. Risk assessments are based on developing MOEs for existing conditions of exposure and showing how they increase with various interventions. Although MOEs are not quantitative risk measures, they provide somewhat better guidance for risk managers than does the inflexible use of RfDs and RfCs. DPR also estimates RfDs and RfCs and calculates air concentrations at specified risk levels so that pesticides can be evaluated as possible toxic air contaminants.

At the same time, the standard defaults for uncertainty factors can be invoked for comparison with MOEs, and analysis can focus on identifying the ranges of MOEs that are clearly inadequate to achieve health protection, probably at least what is needed to achieve health protection, and probably adequate to achieve health protection but with some degree of uncertainty. For many decisions, a system of comparing risks associated with various possible interventions in this fashion will be useful. And for many important DPR decisions, comparing the benefits (risk reductions) of different management options is essential. Implementation of the approach described here clearly and transparently and with adequate peer review can improve decision-making.

Another major topic addressed by the Silver Book is cumulative risk assessment, which is the characterization of the combined risks to health posed by multiple agents or stressors. Consideration is given not only to exposure issues, such as aggregate exposure to the same chemical or exposure to multiple chemicals, but to nonchemical stressors, inherent vulnerabilities, population variability, and other effects on disease outcomes. Recommendations were made for collecting information on those issues in the near term and long term in recognition that more work is necessary to improve the methods of performing cumulative risk assessment. A National Research Council report (NRC 2008) on phthalates addresses issues of dose–response assessments in the context of simultaneous exposures to multiple stressors.

EPA has performed cumulative risk assessments of five groups of pesticides: organophosphates, *N*-methyl carbamates, triazines, chloroacetanilides, and pyrethrins/pyrethroids. Those pesticides were grouped on the basis of their common modes of action. The extent to which DPR has considered such cumulative risk assessments is unclear, but the agency has collected some data that would be relevant to informing them; for example, exposure data on multiple pesticides are available from DPR's air-monitoring and residue-monitoring programs for pesticides. As stressed in the Silver Book, problem formulation is critical for determining the level of complexity and quantification that would be needed for a cumulative risk assessment in light of the decision context.

Lessons from Other National Research Council Reports

National Research Council reports published after the Silver Book provide more detailed guidance on how to address issues raised in it. Most notably, recommendations for improving the

[3]It is often stated that these values are not truly "bright lines", but they are used as though they were, and risk managers cannot treat them in any other way without being accused of manipulating risk-assessment outcomes.

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hazard identification and dose–response analyses of chemicals may be found in *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (NRC 2011) and *Review of EPA's Integrated Risk Information System (IRIS) Process* (NRC 2014). Chapter 7 of the formaldehyde report outlined a "roadmap to revision" of future IRIS documents, which included recommendations for making improvements in four broad categories: descriptions of methods and criteria for selecting studies, approaches to evaluating critical studies, weight-of-evidence analyses, and justification of modeling approaches (NRC 2011). The later report on the IRIS process expands on those recommendations, emphasizing the need to incorporate systematic review principles into the process (see Figure 3-2). The key factor is that the questions to be addressed and the methods by which the scientific evidence will be identified, analyzed, and integrated to answer the questions are set forth in advance of performing the assessment. The goal is to provide an objective analysis through a transparent and standardized approach that allows understanding of how decisions are made at each step of the process (NRC 2014).

CALIFORNIA'S RISK-ASSESSMENT PRACTICES

The committee reviewed DPR's risk-assessment guidance documents and three examples of recent pesticide risk assessments—of carbaryl, chloropicrin, and methyl iodide—for the purpose of understanding the procedures and practices of DPR (see Appendix B for a list of documents reviewed). The committee's observations in this section are related less to the scientific content and technical conduct of the assessments than to the procedures, assumptions, and guidelines that largely determine the direction and outcome of the assessments. Technical recommendations are provided in Appendix C. How the risk assessments are used and understood by risk managers, decision-makers, and stakeholders was of particular interest. Those factors necessarily impinge on DPR's risk-management and communication processes. It was not within the committee's charge to review those aspects of DPR's responsibilities, but improving the integrity and usefulness of DPR's risk assessments ultimately must involve a consideration of the entire risk-analysis framework used by DPR to integrate risk assessment, risk management, and risk communication.

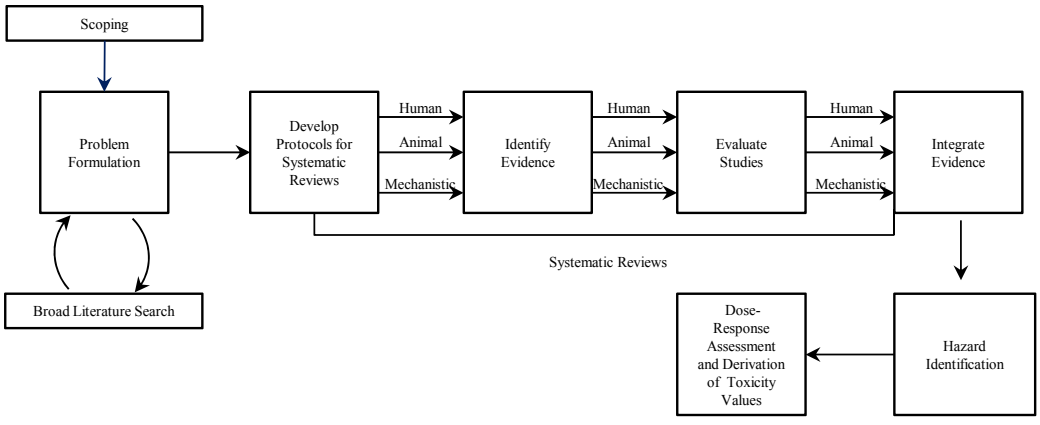

FIGURE 3-2 Systematic review in the context of EPA's Integrated Risk Information System process. Public input and peer review are integral parts of the process although they are not specifically noted in the figure. Source: NRC 2014 (p. 110).

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Strengths

In the risk-characterization documents reviewed by the committee (DPR 2010a,b, 2012), the quality, thoroughness, and depth of the scientific effort put forth by DPR staff are evident. The documents reflect established practices and current trends in regulatory risk assessment as evidenced by several state-of-the-art approaches used to assess dose–response relationships and to model exposure. DPR uses several assets to develop and validate its risk assessments, primarily its collection of California-specific data on exposure, such as data obtained through its Pesticide Use Reporting program, Toxic Air Contaminants Program, and Pesticide Illness Surveillance Program. There is commendable transparency in reporting how hazard identification, exposure assessment, and risk characterization are performed for the assessments. However, it is sometimes less evident why a given procedural approach or assumption is used (see discussion later in this chapter). The risk-appraisal chapters are a particularly good feature of DPR's risk-characterization documents and can be further strengthened to lend integrity to the risk findings by including an even more robust discussion of critical assumptions and inconsistencies with other agencies.

Potential Improvements

Problem Formulation

DPR's risk-characterization documents have yet to include a formal problem-formulation component that clearly elaborates the purpose and approach of the assessment as recommended in the Silver Book (NRC 2009). As discussed earlier in this chapter, developing the problem formulation in conjunction with risk managers would allow risk-assessment results to be understood better in the proper framework for risk management. The problem should be formulated in a way that addresses the decision-making context in which the risk findings are to be applied. Many of the committee's concerns about improving the risk-assessment process would be lessened if a problem-formulation description were developed for each assessment and included a conceptual model and analysis plan. There should continue to be separation between risk assessors and managers with respect to influence on the outcome of an assessment, but joint planning in the early stages of the process to identify and formulate the needs of the risk manager is likely to improve both the relevance and the efficiency of the assessment.

Hazard Identification

In the risk-characterization documents reviewed by the committee, the hazard-identification section often describes extensive post hoc analysis of studies. Independent reanalysis of data is an important aspect of study review that may identify end points otherwise overlooked in the original study and that may additionally help to resolve questionable findings. Post hoc analyses, however, must be conducted with caution or avoided because they might involve inferences that extend beyond the original intent of a study and the scope of problem formulation. When conducted, reanalysis of data should show a dose–response relationship, reproducibility, association with relevant effects that reflect the original study intent (for example, clinical signs or histopathology), differences outside the normal range of variation, and biologic plausibility (Doull et al. 2007). Adherence to such criteria was not uniformly evident in the analyses reviewed by the committee; this might reflect a lack of clear guidance for post hoc analysis of otherwise compliant studies. That can lead to the use of an indicator of exposure (such as ocular irritation in humans or respiration-rate effects in human or animal studies) that has an ambiguous biologic relationship to a toxicologic response (e.g., DPR 2012).

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In addition to toxicologic end points, an indicator of exposure, such as ocular irritation, might have important application as a risk-management tool to mitigate against toxicologically significant exposures. Chloropicrin (DPR 2012) is a case in point. It may be used as a fumigant or as a warning agent added to other pesticide formulations to serve as an indicator of a potentially hazardous exposure to a formulation. It is important for the purposes of risk management and risk communication that the distinction in applying an exposure end point vs a toxicity end point be clear. Otherwise, the public may come to believe that evidence of exposure (ocular irritation or odor detection) represents toxicity. DPR should endeavor to make the nature of the end point clear and to distinguish risk options to prevent misinterpretation.

Recursive evaluation that involves iterating between end-point selection and calculation of an RfC is an inappropriate means of data analysis that favors sensitivity in end-point selection over uncertainty in the findings. In the example of chloropicrin, DPR (2012) analyzed a nonguideline human study with benchmark-concentration methods to identify points of departure for ocular irritation and increased nitrogen monoxide in nasal air. Ocular irritation was the more sensitive effect and had lower uncertainty associated with its RfC. However, DPR chose to use the lower RfC derived on the basis of increased nitric oxide in nasal air even though it was less sensitive than ocular irritation and was associated with greater uncertainty. DPR should consider how to communicate the balance of risk vs uncertainty in the available data and analysis so that risk managers can make clearly informed decisions.

Carcinogenicity risk assessments should use the most up-to-date guidance and be based on a WOE approach. Use of statistical reanalysis and trend analysis should conform to accepted practice and terminology, such as that of the International Agency for Research on Cancer or EPA (2005).

Exposure Assessment

DPR considers several types of potential exposure scenarios for pesticides, such as occupational exposure (for example, in application and harvesting), industrial exposure, residential exposure, and other general-population exposures (for example, to dietary and ambient air). Seven guidance documents on how DPR conducts its exposure assessments were provided (see Appendix B). Four of the documents are undergoing revision, including the master guidance document *Guidance for the Preparation of Human Pesticide Exposure Assessment Documents*. The agency noted that exposure data are often lacking, so it must use assumptions and judgments.

DPR has valuable data generated by its air-monitoring network and California-specific worker and residential information, residue data, and pesticide use and sales information. Those important datasets should be the main focus of the risk-assessment process conducted by DPR. Examples of California-specific data noted by the committee include exposure to multiple pesticides common in tank mixtures in the state, high-end seasonal or migrant-worker exposure scenarios, and frequent meteorologic conditions relevant to fumigant applications. When such information is absent or insufficient, the exposure assumptions and approaches used by EPA or other regulatory authorities may be appropriate as surrogate data.

The rationale for some exposure assumptions used by DPR needs to be clearly explained. Such exposure terms as *high end, worst case,* and *maximum realistic exposure* are used throughout documents, sometimes interchangeably and often without definition. Calculation of the probability of occurrence for use in exposure estimates would communicate the degree of conservatism of the exposure assumptions better and would inform regulatory decision-making better. Even when guidance is available, transparency is sometimes lacking. For instance, characterization of exposure of bystanders to airborne contaminants often refers to a 95th percentile exposure estimate (e.g., DPR 2012). The actual guidance is for only one aspect of the exposure estimate—the source concentration—and prescribes an approach that often results in a value greater than the 95th percentile (Frank 2009). Several further assumptions used to calculate the exposure of at-risk persons push well beyond the 95th percentile and postulate a series of circumstances that

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may be individually plausible but collectively are implausible. Improved guidance and problem formulation that describe exposure calculations, probabilities, and definitions would be useful in this regard.

The committee reviewed DPR's dietary risk assessment of carbaryl (DPR 2010a). DPR relied primarily on the US Department of Agriculture Continuing Survey of Food Intake by Individuals (CSFII) to determine food-consumption patterns in the general public. Although the dataset provided national estimates, it might not be representative of the consumption of fruits and vegetables by California residents. (Data collection for CSFII has been discontinued.) It would be preferable to use California-specific consumption data to the extent possible to provide more representative dietary exposure assessments by collecting data or finding other sources of data. DPR will have to continue to rely on national surveys and models, so it is important for it to stay current with scientific developments and workgroups for exposure modeling, such as the updated Dietary Exposure Evaluation Model—Food Commodity Intake Database/Calendex model. For occupational scenarios, DPR relies primarily on the Pesticide Handler Exposure Database (PHED). Although PHED is standard in occupational-pesticide risk assessment, it is constrained by outdated assumptions. DPR should consider evaluating the utility of the data in the Agricultural Handler Exposure Task Force database to inform its exposure assessments.

DPR has adopted advanced methods of physical modeling to characterize exposure of workers and residential bystanders on the basis of data from application-site mass flux studies (in the case of agricultural fumigation) and site monitoring (in the case of structural fumigation). The models are often applied in such a way as to establish worst-case exposures. In the committee's review of the chloropicrin document (DPR 2012), examples of frequent application of worst-case assumptions included scaling to maximum theoretical flux, using default worst-case weather, fixing the wind rose to expose people continuously throughout an exposure interval, and fixing the position of an exposed person throughout the duration of exposure. To place worst-case exposure outcomes into context, DPR might consider including comparative exposure calculations that are based on more realistic or "typical" exposure scenarios. Including such comparisons would provide risk managers with useful information regarding options for mitigation when worst-case exposure outcomes yield evidence that warrants concern in risk characterization. There is an additional opportunity to use the same modeling approaches in fully stochastic modeling to account comprehensively for available information, such as actual use-rate statistics from pesticide-use reporting databases, the wind rose of distribution of the pesticide off-source, the variation in key weather period driving off-source movement, and the movements and duration of exposure of workers and residents in the immediate vicinity of application sites.

Risk Characterization

DPR makes a number of conservative assumptions and decisions in the performance of its risk assessments. The conflation of a series of conservative assumptions and estimates regarding health effects thresholds and exposures and the application of uncertainty factors can result in scenarios that are well in excess of worst-case exposure even if each individual estimate in itself is scientifically defensible. There appears to be a tendency for that to occur in the DPR assessments, at least in the three documents reviewed by the committee (DPR 2010a,b, 2012). Clarification of the outcomes of these worst-case scenarios can be achieved through comparison to a base case. Risk assessors serve the interests of risk managers best if they also provide a reasonably central view of the level of risk (for instance, a typical-exposure scenario) with an estimate of the range of uncertainty that would indicate the potential for greater risk in more serious situations.

An option would be the more consistent use of stochastic forecasts. Alternatively, information on markets, uses, and demographics can more specifically describe the at-risk people and the uses, markets, and operations that contribute most to risk to help to ascertain the degree to which the combination of various assumptions leads to plausible risk scenarios.

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Consistency in the Department of Pesticide Regulation's Risk Assessments

Although the risk assessments performed by DPR demonstrate the use of established risk-assessment methods, their application is sometimes inconsistent and could be strengthened with clearer guidance that is strictly adhered to. For example, in establishing hazard and regulatory end points, a benchmark dose (BMD) and a lower 95% confidence limit of the benchmark dose (BMDL) are sometimes calculated and used by DPR as relevant points of departure. However, the benchmark response level chosen for the BMD and the BMDL varies from case to case. The risk-characterization document on chloropicrin uses 1%, 2.5%, 5%, and 10% response levels (DPR 2012). That can lead to inconsistency in end-point comparisons between different critical effects. In addition, caution should be used in extrapolating far below the observed range of data because it introduces uncertainty into the assessment. The approaches used are clearly within the bounds of DPR's recommended practices (DPR 2004a,b); however, for uniformity in comparisons among studies and for better understanding of end-point selection, it is advisable that when BMD approaches are used they be applied to all representative studies in a class. There are reasons for the differences in selection of models and thresholds, but the Silver Book points to the difficulty of using results of such analyses given the use of different models and model assumptions to characterize the model uncertainty associated with the BMD approach. DPR's rationale for selecting models is sometimes stated as seeking a more health-protective outcome, which is a judgment with an obscure scientific basis. In fact, there is a tendency in DPR's risk-characterization documents to intermix application of uncertainty factors (a quantifiable assumption based on accepted practice) and health-protective assumptions. Clear guidance and documentation as to the approaches to and assumptions regarding such determinations would improve consistency and increase the integrity of the assessment outcome. For instance, given that DPR now has over a decade of experience working within its guidance for BMD modeling, a revision and clarification of the guidance may be warranted.

DPR has a number of internal and external sources of risk-assessment guidance, but no overarching framework that instructs the DPR assessor as to the appropriate use and application of specific methods and guidelines appears to be available. Such a framework would help to ensure consistency among the risk-characterization documents. It is important that the most up-to-date guidance documents be used and that deviations from them be documented and justified. The dates on DPR's risk-assessment guidance documents (see Appendix B) indicate that they have not been updated regularly and so do not reflect changes that might be necessary in response to recommendations of the Silver Book, EPA, or other resources. Examples of DPR deviations from EPA guidelines include those in study selection, in the use of BMD approaches, and in the WOE approach to evaluate carcinogenicity.

Relationship with the US Environmental Protection Agency

The requirements and procedures for the risk-assessment process in general appear to be similar between DPR and EPA, and the technical barriers to collaboration in risk assessment seem minimal. Although there are formal collaborative processes, it was not clear to the committee how extensively they were used and how effective they were. In the risk assessments considered by the committee, there appeared to be a recent tendency to "second-guess" EPA's risk assessments and to find somewhat higher levels of risk. That can preclude harmonization later when DPR's assessments are provided to EPA for comment. There is a clear need to understand differences between DPR and EPA outcomes with respect to risk assessments of the same pesticide.

Reference values from historical (before 1996) and recent (2004–2010) pesticide-toxicity evaluations by DPR and EPA are compared in Figure 3-3. The data indicate a trend in DPR's estimating higher levels of toxicity than EPA for the same compound in more recent years. In

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1996, CalEPA compared the reference values estimated by DPR and EPA for 39 pesticide AIs (RAAC 1996). It found that DPR selected the same values as EPA for 10 pesticides, lower values (higher toxicities) for nine, and higher values (lower toxicities) for 20. The top histogram of Figure 3-3 shows the distribution of differences in chronic reference values estimated by the two agencies. A difference of a factor of 5 or more was found for 10 pesticides. In seven of those cases, DPR's reference value was higher than derived by EPA; this indicates an estimate of potency lower than that of EPA for the end point in question. DPR estimated values that were lower than EPA's by more than a factor of 2 only 13% of the time. Thus, the two agencies agreed within narrow limits most of the time, and DPR rarely concluded that the toxicity of an AI was much higher than judged by EPA.

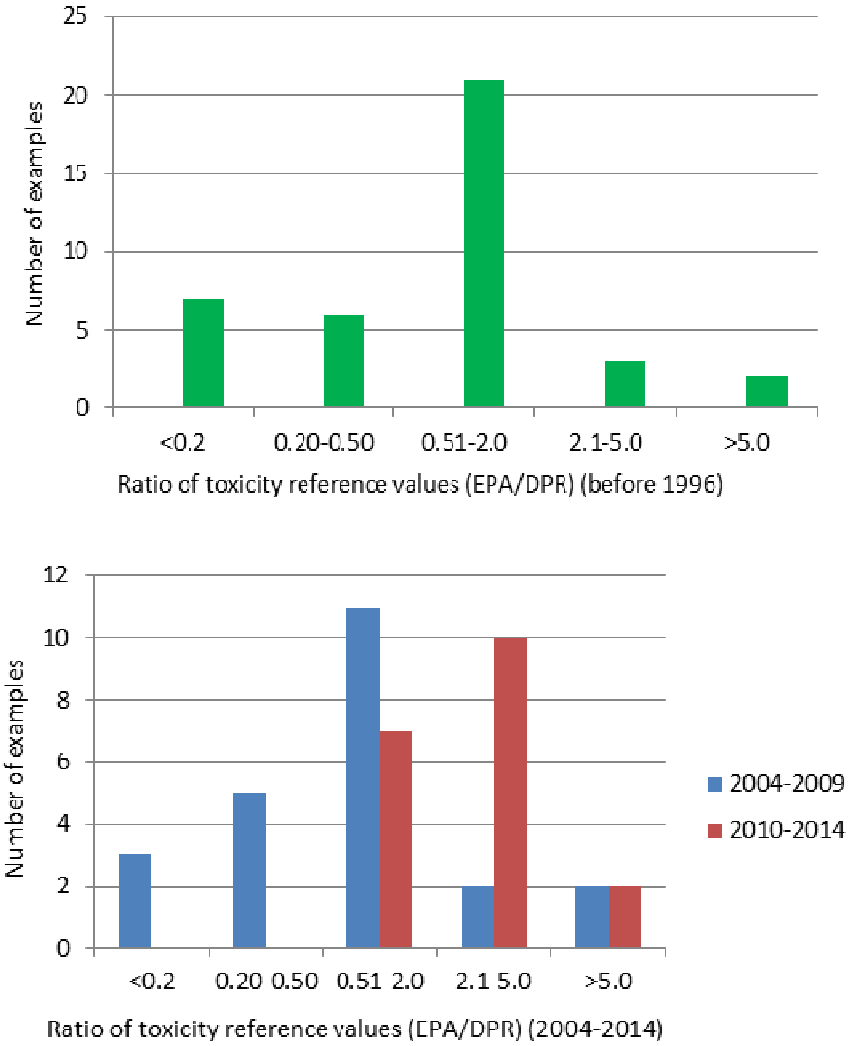

FIGURE 3-3 Comparison of reference values derived by EPA and DPR for the same active ingredients over three periods: before 1996, in 2004–2009, and in 2010–2014. The results in the upper panel compare chronic reference values for 39 active ingredients (RAAC 1996). The data in the lower panel reflect multiple comparisons of reference values for each of 11 active ingredients, including acute, subchronic, and chronic durations and different routes of exposure (see Appendix D).

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DPR provided the committee with a comparison of 11 of the most recently completed pesticide assessments, which spanned 2004–2014 (G. Patterson, DPR, personal communication, July 1, 2014).[4] In the six assessments completed during 2004–2009 (see bottom histogram of Figure 3-3), DPR agreed with EPA within reasonably narrow limits in many cases and in some cases calculated reference values that were higher than those established by EPA. DPR estimated reference values that were lower than EPA's by more than a factor of 2 only 17% of the time. This percentage is similar to that found in the comparison of older pesticide assessments. However, in the five assessments completed during 2010–2014, DPR disagreed with EPA more often than it agreed, and in each of these cases its reference values were lower than those of EPA (ratios greater than 1); this indicates a higher estimate of potency than made by EPA. Although the number of samples for the comparisons is small, it raises the question of whether there has been a recent divergence between DPR and EPA in toxicity assessments. That possibility is supported by the observation of similar trends in the cancer characterization and potency estimates derived by the two agencies for the same 11 AIs and in DPR's risk-characterization documents for methyl iodide (DPR 2010b)[5] and chloropicrin (DPR 2012).[6] In the assessments conducted before 2010 (see Appendix D), DPR disagreed with EPA on the carcinogenicity and potency estimates in only one of the six cases; in the one case, DPR considered methidathion to be a carcinogen whereas EPA did not. In the assessments conducted since 2010, DPR disagreed with EPA in four of seven cases, either judging that the AI should be treated as a carcinogen (methyl iodide, chloropicrin, and simazine) in contrast with EPA or calculating a significantly higher cancer potency (by more than a factor of 10 for carbaryl) when the agencies agreed on the carcinogenic nature of the pesticide. Box 3-1 examines DPR's cancer risk assessment for carbaryl in comparison with those of other relevant organizations. DPR was the only one of six organizations that found an unacceptable cancer risk associated with dietary exposure to carbaryl, primarily because it estimated the highest cancer potency.

Overall, DPR has generally estimated reference values within a factor of 5 of those established by EPA and rarely estimated toxicity greater than a factor of 2 above EPA. The magnitude of such differences lies within the normal bounds of uncertainty inherent in such assessments and raises the question of whether EPA's reference values and cancer potencies could be satisfactory for use by DPR in many risk assessments unless DPR has new toxicology studies that were not considered by EPA (which does not appear to be the case in the 11 recent examples) or has compelling evidence to question EPA's estimates. Accepting EPA assessments as a default practice in the absence of a clear and pressing rationale for repeating the hazard identification and dose–response characterizations could save large amounts of staff effort and improve efficiency. There should rarely be a need to conduct an independent assessment. The Silver Book states that "the goal of timeliness is as important as (sometimes more important than) the goal of a precise risk estimate" (NRC 2009, p. 20). For the purposes of the present report, recommendations to rely on EPA's hazard identification and dose–response estimates to a greater extent does not equate to relying on the overall risk estimates inasmuch as exposure must also be considered; there may be important California-specific exposure scenarios that differ from those for the general US population used by EPA.

Although scientists can disagree on scientific interpretation, the consideration of general factors (such as definitions of terms, application of uncertainty factors, approaches for identifying a threshold, and default parameters for exposure calculations) may become largely a matter

[4]The assessments of methyl iodide and chloropicrin were completed in 2010 and 2012, respectively, but were excluded from DPR's submission because they were among the example assessments being reviewed in depth by the committee.

[5]DPR estimated a Q* factor of $0.2–3.2 \times 10^{-2}$ for methyl iodide, but EPA judged it not to be a carcinogen.

[6]DPR estimated a Q* factor of 1.6×10^{-2} for chloropicrin, but EPA judged it not to be a carcinogen.

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of policy. However, the general factors should be similar more often than dissimilar when risk assessments are undertaken by recognized regulatory authorities. Genuine differences in toxicity assessments (even small differences in magnitude) should not be minimized in the interests of harmonization between regulatory agencies, but consideration should be given to the benefits of harmonizing approaches among DPR and sister agencies, especially EPA, in terms of such factors as conservation of regulatory resources, enhanced public confidence in the risk-assessment process, possible interstate trade barriers, and the availability to California growers of pesticides that are used by growers in other states. When harmonization is impossible because of policy issues, the reasons for the differing approaches must be clearly elaborated and defended. In several instances, risk appraisals clearly point out the differences but do not elaborate on why the differences exist and why they were intractable.

BOX 3-1 Cancer Assessments of Carbaryl Performed by Different Organizations

The committee examined the cancer risk assessments of carbaryl by DPR (2012), the International Programme on Chemical Safety (IPCS 2001), EPA (Fort 2003, 2007), the European Food Safety Authority (EFSA 2006), the Australian Pesticides and Veterinary Medicines Authority (APVMA 2007), and Health Canada (2009). It found that although all the organizations used the same study as the basis for calculating cancer potency and agreed on the critical end point derived from the study, they derived different estimates of cancer risk. DPR, EPA, and Health Canada used nonthreshold linear extrapolations to derive Q* cancer potency factors. The differences in the values appear to be due in part to judgments about whether to include the high-dose data from the study and whether to combine findings on hemangiosarcomas with those on hemangiomas. DPR excluded the high-dose data and combined the tumor types to derive a Q* value (9.72×10^{-3} mg/kg-day), which is about 11 times higher than that derived by EPA (8.75×10^{-4} mg/kg-day); the latter included the high-dose data and considered only hemangiosarcomas. Like DPR, Health Canada excluded the high-dose data and combined the data on hemangiosarcomas and hemangiomas but calculated a Q* value (1.08×10^{-3}), which is only slightly above that of EPA. On the basis of those results, only DPR concluded that dietary exposure to carbaryl carries an unacceptable cancer risk (about 3×10^{-6}). The reason for the discrepancies in Q* values and resulting judgments on the acceptability of the cancer risk are not obvious, because the processes used by EPA and Health Canada are not fully explained, but the differences reveal a lack of consensus and considerable uncertainty in this element of the risk assessment.

The International Programme on Chemical Safety, the European Food Safety Authority, and the Australian Pesticides and Veterinary Medicines Authority used a different (threshold) approach to estimate cancer risk that was based in part on their conclusion that the WOE did not indicate that carbaryl is genotoxic. An acceptable daily intake (ADI) of 0.008 mg/kg-day, which was based on a safety factor of 2,000, was determined by each of those agencies. The highest chronic dietary exposure of various groups to carbaryl estimated by DPR under California conditions is 0.000379 mg/kg-day, which is less than 5% of the ADI and indicates no basis for concern if this alternative approach had been used. Thus, of the six agencies included in this comparison, only DPR calculated a cancer potency that leads to the conclusion that dietary carbaryl presents an unacceptable risk.

The committee points out the discrepancies not to suggest that DPR's conclusions fall outside the reasonable bounds of scientific analysis (in fact, DPR has carefully justified its conclusions) but to illustrate DPR's tendency toward conservatism. They also raise a question about whether any attempts at harmonization between EPA and DPR were made. Finally, despite DPR's discussion of sources of uncertainty, its summary and conclusions do not indicate the considerable level of uncertainty and the degree of confidence that DPR has in its conclusion about the existence of an unacceptable cancer risk.

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Productivity and Efficiency of the Department of Pesticide Regulation's Risk-Assessment Process

Although DPR's risk-assessment methods are technically advanced, the resulting time and effort expended by the agency's personnel on independent assessments of single compounds is probably not sustainable in view of the current workload, including the required re-evaluation of high-priority AIs. DPR needs to consider the important aspect of timeliness of its risk-assessment process with respect to health and safety. DPR provided the committee with the timelines for completion of its risk-characterization and exposure-assessment documents for select AIs completed in 2000–2013. Twelve completed risk-characterization documents were listed for those years. The typical amount of time to complete the assessments was 6–10 years; the shortest took 2 years (DEET), and the longest took 19 years (azinphosmethyl). Three more documents were in the final stage of completion (submitted to the assistant director of DPR in 2014); the amount of time it took for them to reach this stage was 7–16 years (G. Patterson, DPR, personal communication, July 1, 2014). Turnovers in staff, competing responsibilities of risk assessors, and problems in coordinating assignments have contributed to the length of time needed to complete some assessments. Of the 11 most recently completed assessments, the committee noted that a few were of AIs that had no active registrations or uses at the time of completion (for example, methamidophos and methyl parathion).

DPR could substantially streamline its process and achieve greater productivity by relying on external-agency information (primarily from EPA's Office of Pesticide Programs) for some components of the risk assessment to avoid duplication of effort. For example, in some cases, hazard identification and dose–response analysis conducted by EPA appear to be conducted in parallel, and not collaboratively, with DPR. Whether performing an independent risk assessment is the best use of DPR's resources to ensure occupational and public health protection is unclear. If the agencies are reviewing the same studies and using the same or similar guidelines, the hazard findings should be similar, and it might be possible for DPR to leverage the hazard identifications developed by EPA. DPR might well consider how pesticide risk assessments in other states (such as New York and Florida[7]) are conducted in the context of resource constraints and leverage information on pesticides that have been evaluated by other regulatory authorities. If statutory requirements in California dictate specific health-protective approaches, they need to be highlighted on the basis of policy, and assessments by other regulatory authorities would need to be adjusted in keeping with those clearly stated policies. If DPR is able to rely on EPA's assessments, it could direct more resources to California-specific needs, such as better characterization of exposure scenarios and estimates, when it lacks the ability to use assessments from other regulatory authorities or national estimates are inappropriate. In addition, DPR could potentially complete the assessments of more pesticides each year.

When DPR produces its own independent risk-characterization documents, efforts should be made to streamline the documents and the internal reviewing procedures. DPR's risk-characterization documents often repeat information within and among assessments, such as hazard identification from an earlier assessment. That poses a problem for both timely conduct and communication of risk assessments. Internal processes in DPR need to be established to limit repetitive information and staff time spent on generation and review of sections. It is the committee's judgment that the current redundancy in risk assessments conducted by DPR, in conjunction with limited resources and workflow constraints, is affecting DPR's ability to complete risk assessments in a timely manner. Streamlining the scope of and approach to conducting risk assessments would present opportunities to refine the agency's priority-setting process as well (see Chapter 2).

[7]New York and Florida used to perform their own pesticide risk assessments but now rely on EPA's risk assessments (A. Lawyer 2014).

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Furthermore, DPR could cease work on a risk-characterization document if the registration status and use of the pesticide have changed to such an extent that public and occupational health risks are no longer of concern. That would allow DPR to refocus on currently used pesticides and pesticides of emerging concern.

FINDINGS AND RECOMMENDATIONS

On the basis of its review of three relatively recent risk-characterization documents, the committee found DPR risk assessments to be comprehensive, clear, and technically sound. The documents reflect that DPR staff is attempting to follow best practices in risk assessment and making a particularly valuable contribution in state-specific exposure assessments. However, the committee was struck by what appears to be an enormous duplication of effort in DPR's conduct of toxicologic assessments of individual pesticides independently of EPA. The magnitude of differences in reference values estimated by the agencies for the same compound generally falls within the normal bounds of uncertainty. Although mechanisms are in place for collaboration between the two agencies, it appeared that harmonization is not regularly achieved. In the committee's judgment, there are considerable benefits to harmonizing approaches among DPR, EPA, OEHHA, and other relevant agencies. The exposure assessments performed by DPR provide the greatest benefit when they introduce state-specific considerations into the risk-assessment process.

Recommendation: *DPR should review the legislative mandates under which it works to determine whether an independent comprehensive evaluation of pesticides is required in every case in which a risk assessment is performed. If no new and compelling toxicology data have been generated since an EPA assessment was conducted and if there is no reason to believe that the EPA assessment is seriously flawed, DPR could rely on EPA's assessment to a greater extent. If the legislation allows, DPR should collaborate with EPA on its pesticide risk assessments and then rely on EPA's hazard identification, dose–response assessment, and derivation of reference values as a starting point for its own evaluations and focus its efforts on collecting California-specific exposure data, which will help in tailoring the risk assessments to the state's needs. Some data might be obtained from other groups or researchers that are collecting exposure information in the state, but the agency may still be required to collect its own data.*

When independent assessment is warranted, it will be important for DPR risk assessors to keep abreast of the risk-assessment recommendations outlined in recent National Research Council reports and relevant guidance developed by other agencies, particularly EPA, on how the recommendations can be implemented.

Recommendations:

- *DPR should undertake a careful review of the framework presented in Chapter 8 of the Silver Book (NRC 2009) and the practical guidance in EPA (2014) and NRC (2014) for improving risk assessments. The review should include collaboration between risk assessors and managers to ensure a common understanding of the definitions, principles, and steps of the risk-assessment process, including stakeholder involvement.*
- *DPR should incorporate problem formulation and other relevant elements recommended in the Silver Book into its risk-assessment process. An important consideration is that risk managers should be involved in the problem-formulation stage so that risk assessments can be designed to address the decisions that need to be made by the managers and other stakeholders. Consideration should be given to whether a general set of problems and risk-management options could be formulated to use as a starting point in problem formulation.*

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- *DPR should update its risk-assessment guidance documents regularly to reflect the most current risk-assessment practices. The guidance documents could draw from the work of EPA, OEHHA, and other relevant agencies; this could help to standardize and streamline reviews and evaluation approaches and promote consistency among the assessment teams and contributors. It might be useful for DPR to develop an overarching framework for considering and applying the various guidance documents on which it relies to ensure consistency between risk assessments and to aid new risk-assessment staff.*
- *DPR should update its guidance on defaults and begin developing explicit guidance on the inclusion of missing defaults, such as defaults for human variation in susceptibility to cancer and for risks to susceptible subpopulations (during early life and other stages). Guidance should also be developed on when departures from defaults may be justified.*
- *DPR should ensure that risk-management documents arising from its risk appraisals discuss explicitly how an appraisal informed a decision and describe the uncertainties associated with the assessment. A useful resource is draft guidance from EPA (2014), which discusses four principles (transparency, clarity, consistency, and reasonableness) to ensure the usefulness of information in the risk-characterization step to risk managers.*
- *In the long term, DPR should monitor (and perhaps participate in) the activities of EPA and OEHHA in developing guidance on unified approaches to performing quantitative risk assessments for cancer and noncancer end points and in performing cumulative risk assessments. DPR scientists should stay abreast of current trends in exposure assessment, perhaps by having opportunities for specialized training, participation in scientific conferences, and engagement with workgroups and task forces that advance the science of exposure assessment.*

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4

California Data to Inform Priority-Setting and Risk Assessment of Pesticides

As noted in Chapter 3, the committee judges that the California Department of Pesticide Regulation (DPR) may be able to rely more on the toxicologic assessments performed by the US Environmental Protection Agency (EPA) and therefore direct more resources toward obtaining California-specific data on pesticide uses, exposure, and illnesses. Focus on the latter will allow DPR to factor California-specific data into its risk assessments—such as information on cropping patterns, agricultural practices, agricultural–urban boundaries, characteristics of agricultural workers, and population demographics—to a greater extent. The purpose of this chapter is to identify where further data-gathering by DPR might help to improve its priority-setting and risk-assessment processes.

PESTICIDE-EXPOSURE INFORMATION

In many circumstances, EPA and DPR use generic exposure scenarios and national estimates in their exposure assessments of pesticides. For example, in estimating exposure to pesticides, they use sources of data on pesticide residues, such as the US Department of Agriculture (USDA) Pesticide Data Program; on dietary intakes, such as the USDA Continuing Survey of Food Intake by Individuals and the National Health and Nutrition Examination Survey (NHANES); on specific handler exposure scenarios, such as the Pesticide Handler Exposure Database, the Agricultural Handlers Exposure Database, and the Outdoor Residential Exposure Task Force; and on other relevant issues such as Agricultural Reentry Task Force Transfer Coefficients. DPR supplements exposure assessments with California-specific information, which the committee judges to be the most valuable contribution to DPR's risk-assessment process. California routinely collects data on agricultural and other pesticide uses, air concentrations of pesticides, and reports of human pesticide-related illnesses.

California Pesticide Use and Ambient-Air Concentrations

California was the first state to require reporting of agricultural pesticide use. The Pesticide Use Reporting (PUR) program is recognized as one of the most comprehensive in the nation. All agricultural pesticide use must be reported monthly to county agricultural commissioners, who report the data to DPR. The reporting requirements also include pesticide applications in public areas, rangeland, and pastures; postharvest pesticide treatments of agricultural commodities; and pesticide treatments in poultry and fish production and in some livestock applications. Data are typically compiled into square-mile areas (meridian–township–range sections), but initiatives have been undertaken to encourage the use of geospatial information systems to improve the spatial resolution of pesticide applications to smaller areas, such as field sites. Pesticide applications in home and garden use and in most industrial and institutional uses are excluded from the

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reporting requirements (DPR 2013). Although it would be difficult to obtain accurate information on personal home use, it might be possible to collect some information by expanding PUR reporting requirements to cover all licensed pesticide appliers, including those who perform applications for nonagricultural purposes at homes, institutions, and industries. There appears to be no requirement to report the use of pesticide-treated seeds.

The California Air Resources Board (ARB) collects measurements of ambient pollutants from over 40 sites in the state. DPR and ARB monitor pesticides that have been deemed toxic air contaminants. Two types of monitoring data are collected: on ambient monitoring and on application-site monitoring. Ambient monitoring is performed in selected communities to measure pesticide concentrations over several weeks or months, and application-site monitoring is performed in the immediate vicinity of specific pesticide applications to measure concentrations over hours or days.

PUR and ARB data have been used by DPR and other researchers to evaluate the agricultural use of pesticides and ambient concentrations (e.g., Harnly et al. 2005; Li et al. 2005) and to evaluate the predictive capability of exposure models (e.g., Cryer 2005; van Wesenbeeck et al. 2011). Most recently, the California Environmental Health Tracking Program studied agricultural pesticide use near public schools (CEHTP 2014). PUR data have also been used by researchers to investigate the relationship between pesticide exposure and a variety of health outcomes, such as fetal death (Bell et al. 2001a,b), lowered birth weight (Gemmill et al. 2013), birth defects (Shaw et al. 2014; Yang et al. 2014), childhood autism (Roberts et al. 2007), Parkinson disease (Costello et al. 2009; Manthripragada et al. 2010), and childhood and adult cancers (Gunier et al. 2001; Clary and Ritz 2003; Marusek et al. 2006). Although epidemiologic studies do not establish causal relationships, they might be used to identify potential health outcomes of concern.

California Dietary Intake

The use of NHANES data and other national or generic sources of data on dietary consumption may not accurately reflect the dietary patterns of the state, in that they do not take into account demographics, seasonal availability of produce, or other factors specific to California. There are a number of dietary studies of California residents, which might provide confirmatory evidence of the adequacy of NHANES data for risk-assessment purposes. For example, the committee found a few California-specific surveys from the Centers for Disease Control and Prevention (CDC 2010, 2012) and the California Department of Public Health (CDPH 2010, 2011a,b) that provide broad characterizations of Californians' consumption of fruits and vegetables.

Similar to the need to incorporate or use California-specific information on dietary consumption, DPR should seek ways to leverage its programs and expertise to generate state-specific information on drinking-water intake patterns to reflect source-water typography and meteorology, demographics, or spatiotemporal patterns relevant to an exposure assessment. To the extent possible, DPR should partner with other agencies and organizations to obtain state-specific estimates of drinking-water consumption and the concentrations of evaluated pesticides in drinking water to develop customized and site-specific exposure assessments for this pathway.

California Worker Scenarios

Because of the types of agriculture in California and its climatic conditions, general nationwide assumptions about seasonal use of pesticides, the number of growing seasons, and working conditions may not be appropriate for DPR's assessments. The demographics of the agricultural workforce may also be substantially different from nationwide estimates. The committee heard from stakeholders representing agricultural workers that workers may work over 10 hours per day during the growing season, work with labor-intensive crops, may not have accessibility to showers, and may be adolescents (Katten 2014). Although susceptible populations, such

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as pregnant women and children, are routinely considered in most risk assessments, less consideration has been given to risks to adolescent workers. Adolescents are prohibited from handling pesticides, but they could have exposures different from those estimated for worker bystanders. Thus, better characterization of the worker population and working conditions would help DPR in tailoring its risk assessments.

EPA has an initiative under way to revise its risk-assessment methods for workers, children of workers in agricultural fields, and pesticides that have no food uses (EPA 2009). Proposed changes include consideration of adolescent workers and of workers and their children who may accompany them to work. This presents an opportunity for DPR to collaborate with EPA on these important issues.

Other California Exposure Information

California began an environmental-contaminant biomonitoring program in 2006, and several pesticides are monitored. The program is a collaborative effort of the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment and Department of Toxic Substances Control. Several biomonitoring studies of pesticide exposure have been conducted in California. They have examined contemporary exposures of agricultural workers, other adults, and potentially susceptible subpopulations (such as pregnant women and children) primarily to organophosphates. Estimates have been based on samples of urine (e.g., Castorina et al. 2003; Bradman et al. 2005, 2007; Trunnelle et al. 2014a), breast milk (e.g., Weldon et al. 2011), blood (e.g., Huen et al. 2012), teeth (e.g., Gunier et al. 2013), and amniotic fluid (e.g., Bradman et al. 2003). A number of the studies are going on now and are being conducted in collaboration with the California Biomonitoring Program. In addition, a workgroup of EPA's Pesticide Program Dialogue Committee (21st Century Toxicology/New Integrated Testing Strategies Workgroup) is developing a priority list of pesticides for biomarker research, working to identify how existing data relevant to diagnosing overexposure to pesticides can be made more accessible, and working to identify opportunities for additional information (EPA 2014).

California-specific data on environmental exposure to pesticides are also being collected. Some data are available on pesticide residues on foliar samples, soil, dust, surface or hand wipes, and other environmental materials (e.g., DPR 2009; Harnly et al. 2009; PANA 2010; Gunier et al. 2011; Trunelle et al. 2014b). The evaluations have been performed in homes, in schools, and in the field. It might be useful for DPR to review the scientific literature periodically for relevant information and new developments that could inform its exposure assessments.

Surveillance of Pesticide-Related Illness

Since 1971, California has been mandated through DPR to maintain the Pesticide Illness Surveillance Program (PISP), the oldest and largest program of its kind in the United States. Cases of human pesticide-related illness are required to be reported within 24 hours of examination. Cases are reported by five mechanisms: a clinician reports a suspected case to a local health officer, who files an illness report; a clinician calls the California Poison Control System; the worker-compensation system identifies cases; a clinician files a Doctor's First Report of Occupational Illness and Injury form (DPR 2003); or a clinician reports a case on line through the California Reportable Disease Information Exchange system (CDPH 2014). Pesticide-poisoning cases are investigated by the county agricultural commissioner who is responsible for the county in which the poisoning occurred. Another source of case ascertainment is the cholinesterase monitoring program; DPR regulations require employers to provide medical monitoring of workers who regularly handle organophosphate or carbamate insecticides (OEHHA 2007; DPR 2011).

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The following steps are necessary for illness cases to be successfully reported: the affected person must be seen by a clinical provider, the clinician recognizes the condition as a pesticide-related event, the clinician is aware of the requirement to report, the clinician files a report, and the receiving agency records and documents the case. Employees, supervisors, and any members of the public can also bring cases to the attention of the county commissioners. The surveillance program probably underreports the number of pesticide-related illnesses in the state because access to health care for many workers may be inadequate, workers may be reluctant to report illnesses, and clinicians may not have the appropriate training to identify a case as pesticide-related or be aware of the need to report cases. Some cases may also be misclassifications of illnesses unrelated to pesticide exposure.

PISP data can affect the risk-assessment process by affecting priority-setting among active ingredients; pesticides shown to have higher numbers of human health incidents related to their use may be assigned priorities before an equivalent pesticide that has less history of pesticide-related illnesses (S. Koshlukova, DPR, Sacramento, CA, personal communication, May 16, 2014). In addition, PISP data can aid in problem formulation regarding specific pesticides and may confirm risk-assessment findings. CDPH is considering linking data from the PUR and PISP databases to investigate possible correlations (P. English, Environmental Health Investigations Branch, personal communication, July 8, 2014). In the future, opportunities for collecting data on pesticide-related illness from medical records might come from the recent passage of the Health Information Technology for Economic and Clinical Health Act, which promotes the adoption and "meaningful use" of health-information technology.

FINDINGS AND RECOMMENDATIONS

The committee judges that DPR's risk-assessment process could best be improved by more data collection and better characterization of pesticide exposure in the state. Programs are already in place to collect state-specific data, and the efforts might be expanded and coordinated with other departments to fill data gaps.

Recommendations:

- *Consideration should be given to expanding PUR reporting requirements to include licensed pesticide appliers, who would include those who perform applications for nonagricultural purposes in homes, institutions, and industries if not already required to so. The resulting data would help to fill gaps in information about exposure from those types of pesticide uses.*
- *If resources allow, PUR data should be reviewed in relation to air-monitoring data and surveillance data on pesticide-related illness to determine whether any patterns are evident and to judge the accuracy of exposure assumptions or models.*
- *The integration of a component based on a geospatial-information system into the PUR program should continue to be encouraged.*
- *Because surveillance programs like PISP rarely capture more than a moderate percentage of cases, consideration should be given to improving the reporting of pesticide-related illness, for example, by improving training of clinicians, expanding the means by which cases can be reported, searching electronic health records, and possibly expanding the use of biomarkers. More accurate data on pesticide-related illness will support better priority-setting and aid in the development of problem formulation for conducting risk assessments of specific pesticides.*

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Appendix A

Biosketches of the Committee to Review California's Risk-Assessment Process for Pesticides

Marion F. Ehrich (Chair) is professor of pharmacology and toxicology at the Virginia–Maryland College of Veterinary Medicine (VMCVM) and at Virginia Tech Carilion School of Medicine and Research Institute. She is also codirector of the VMCVM Laboratory for Neurotoxicity Studies. Her research interests are in biochemical neurotoxicology, especially neurotoxicity of organophosphorus components, and drug development. Dr. Ehrich is a past president of the Society of Toxicology. She has served on numerous scientific expert panels, including current membership on the US Environmental Protection Agency Federal Insecticide, Fungicide, and Rodenticide Act Science Advisory Panel. She also served on the National Research Council's Committee on Toxicology and its Subcommittee on Toxicologic Assessment of Low-Level Exposures to Chemical Warfare Agents and on the Institute of Medicine's Committee on Gulf War and Health: Review of the Literature on Pesticides and Solvents (Pesticide Panel). Dr. Ehrich received her MS in pharmacology and toxicology from the University of Chicago and her PhD in pharmacology and toxicology from the University of Connecticut. She is certified by the American Board of Toxicology and is a fellow of the Academy of Toxicological Sciences.

Brenda Eskenazi is the Jennifer and Brian Maxwell Professor of Epidemiology at the University of California, Berkeley School of Public Health. She is also director of the Center for Environmental Research and Children's Health and head of the Division of Community Health and Human Development. Her research interests are in the effects of environmental exposures (for example, to pesticides, lead, solvents, dioxin, and tobacco smoke) on reproductive, perinatal, and children's health. Dr. Eskenazi was a member of the Institute of Medicine's Board on Children, Youth, and Families. She received her MA in psychology from Queens College and her PhD in neuropsychology from the City University of New York. She had a postdoctoral fellowship in environmental epidemiology and toxicology at the Yale School of Public Health.

Roberta L. Grant is manager of the Toxicology Section of the Texas Commission on Environmental Quality (TCEQ), where she manages staff conducting toxicologic evaluations of air permit applications, carrying out monitoring projects, and performing risk assessments. She was involved in writing TCEQ's guidelines for developing toxicity factors. She coordinates and is involved in the development of chemical-specific technical support documents to support the development of acute and chronic inhalation toxicity factors. Dr. Grant is also an adjunct professor in the College of Pharmacy of the University of Texas at Austin. She was a member of the US Environmental Protection Agency's National Advisory Committee for Review of Acute Exposure Guideline Levels and has served as an ad hoc member of the agency's Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel. She received her PhD in toxicology from the University of Texas at Austin.

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Robert M. Hollingworth is professor emeritus in the Department of Entomology and the Center for Integrative Toxicology of Michigan State University. His research interests are in pesticide toxicology and mechanisms of toxicity of and resistance to pesticides. He is director of the North Central Region IR-4 Program, which is a 12-state program funded by the US Department of Agriculture that provides data to enable the registration of pesticides on specialty crops with the US Environmental Protection Agency (EPA). He has served on a number of state and national advisory panels related to pesticide issues, including EPA's Federal Insecticide, Fungicide, and Rodenticide Act Science Advisory Panel. He also continues teaching activities on the risk assessment and regulation of chemical contaminants in the diet and the safety of genetically modified foods. Dr. Hollingworth received his PhD in insecticide toxicology from the University of California, Riverside.

Matthew C. Keifer is director of the National Farm Medicine Center. Before joining the center, he was associate director of the Pacific Northwest Agricultural Safety and Health Center of the University of Washington. His research and practice emphasize pesticide health effects and agricultural injury. He is the codirector of the Upper Midwest Agricultural Safety and Health Center, which is funded by the National Institute for Occupational Safety and Health. Dr. Keifer is a member of the US Environmental Protection Agency's Pesticide Program Dialogue Committee. He was a member of the National Research Council's Subcommittee for the Review of the Risk Assessment of Methyl Bromide and of the Institute of Medicine's Committee on Occupational Information and Electronic Health Records. He received his MD from the University of Illinois and trained in internal medicine and occupational medicine, and he received his MPH in public health from the University of Washington.

Chensheng (Alex) Lu is associate professor of environmental-exposure biology in the Harvard School of Public Health. His research interests are in the use of biomarkers for assessing human exposures to environmental chemicals to facilitate the identification of risk factors. His current work involves projects to integrate exposure, metabolomics, and cumulative risk-assessment tools for quantifying children's longitudinal dietary exposure to pesticides. Other research is focused on identifying biomarkers in the gene–environment paradigm in relation to pesticide exposure. He is also collaborating on studies with the Boston Housing Authority to minimize children's residential exposures to pesticides in low-income urban public housing. Dr. Lu serves as an ad hoc member of the US Environmental Protection Agency's Federal Insecticide, Fungicide, and Rodenticide Act Science Advisory Panel and its Food Quality Protection Act Science Review Board. He received his MS in environmental sciences from Rutgers University and his PhD in environmental and occupational health sciences from the University of Washington.

Joseph V. Rodricks is a founding principal of ENVIRON International Corporation. His expertise is in toxicology and risk analysis and their uses in regulation. He was formerly deputy associate commissioner for health affairs and toxicologist for the US Food and Drug Administration. His experience includes chemical products and contaminants in food and food ingredients, air and water pollution, hazardous wastes, the workplace, consumer products, medical devices, and pharmaceutical products. Dr. Rodricks has served on over 30 committees of the National Research Council and the Institute of Medicine, including the Committee on Improving Risk Analysis Approaches Used by the US Environmental Protection Agency. In recognition of his extraordinary contributions to these programs, he was designated a national associate of the National Academy of Sciences. He received his PhD in biochemistry from the University of Maryland and is a diplomate of the American Board of Toxicology.

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David L. Stone is an associate professor in the Department of Environmental and Molecular Toxicology of Oregon State University (OSU). He directs the National Pesticide Information Center, a cooperative agreement between OSU and the US Environmental Protection Agency. He also holds an appointment in Extension Services, where he engages diverse stakeholders on issues related to pesticide exposure, integrated pest management, risk assessment, and risk communication. Dr. Stone has served on several state and national scientific advisory panels and is a past president of the Pacific Northwest Association of Toxicologists. In addition, he teaches courses on toxicology and biotechnology, is a coleader in the Research Translation Core of OSU's Superfund Program, and is an investigator in a Multicultural Scholars Program for underrepresented students. Before joining OSU, Dr. Stone served as a state toxicologist for the Oregon Health Division. He received his MS from the University of North Texas and his PhD in toxicology from OSU.

Jeffrey D. Wolt is professor of agronomy and toxicology in Iowa State University and adjunct professor of epidemiology in the University of Iowa. His research interests are in pesticide and biotechnology safety analysis applied to risk management and science-policy decision-making, soil and environmental chemistry applied to exposure assessment, environmental monitoring, and environmental toxicology. His outreach responsibilities center on risk communication and harmonization of formalized frameworks for risk management and public-policy decision-making. Before joining Iowa State University in 2004, Dr. Wolt was an environmental chemist and risk analyst in industry, where he served as cochair of the Federal Insecticide, Fungicide, and Rodenticide Act Environmental Model Validation Task Force. He received his MS in agronomy and soil science and his PhD in soil chemistry from Auburn University.

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Appendix B

Department of Pesticide Regulation Risk-Assessment Guidance Documents

Priority-Setting and Initiating Risk Assessment

Process for Human Health Risk Assessment Prioritization and Initiation (DPR 2004a)
Final Notice on Active Ingredients Prioritized for Risk Assessment Initiation (DPR 2007)
Prioritization and Status of Active Ingredients for Risk Characterization: Report #52 (DPR 2011a)
Final Recommendations Regarding the List of Active Ingredients Prioritized for Risk Assessment Initiation (Schreider 2014)

DPR Risk-Assessment Guidance

Guidance for Evaluating Genetic Toxicology Studies (DPR 2000)
Guidance for Benchmark Dose (BMD) Approach – Continuous Data (DPR 2004b)
Guidance for Benchmark Dose (BMD) Approach – Quantal Data (DPR 2004c)
A Guide to Pesticide Regulation in California (DPR 2011b)
DPR Risk Assessment Guidance – default uncertainty factors, NOEL and RfC (DPR 2011c, *undergoing revision*)

Exposure-Assessment Guidance

Guidance for the Preparation of Human Pesticide Exposure Assessment Documents (Thongsinthusak et al. 1993, *undergoing revision*)
Interim Guidance for Selecting Default Inhalation Rates for Children and Adults (Andrews and Patterson 2000, *undergoing revision*)
Worker Health and Safety Branch Policy on the Estimation of Short-term, Intermediate-term, Annual, and Lifetime Exposures (Andrews 2001)
Guidance for Determination of Dislodgeable Foliar Residue (Edmiston et al. 2002)
Guidance for Dietary Exposure Assessment (DPR 2009)
Methods for Calculating Short-term Exposure Estimates (Frank 2009a)
Exposure Assessment Policy and Procedure – Default Transfer Coefficients (Frank 2009b, *undergoing revision*)
Surrogate Handler Exposure Estimates for Use in Assessments by the California Department of Pesticide Regulation (Beauvais et al. 2007, *undergoing revision*)

Air Monitoring and Methods

Examples of DPR's recommendations for an ambient monitoring study and ARB's protocol:

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Use Information and Air Monitoring Recommendations for 1,3-Dichloropropene, Methyl Bromide, Chloropicrin, and Methyl Iodide (Oros and Neal 2010)
Sampling Protocol for 1,3-Dichloropropene, Methyl Bromide and Methyl Iodide Ambient Air Monitoring (Adler 2011)

Examples of DPR's recommendations for an application-site study and ARB's protocol:
Use Information and Air Monitoring Recommendation for Chlorthal-Dimethyl (Mullane 2010)
Sampling Protocol for Chlorthal-Dimethyl (Dacthal) Application Study (Aston 2011)

Modeling procedures to estimate fumigant air concentrations for exposure assessment:
Development of Sub-chronic Air Concentration Estimates Associated with a Single Fumigant Application (Barry 2008a)
Screening Level Air Concentration Estimates for Worker Health and Safety Exposure Analysis (Barry 2008b)

Example Risk Assessments

Chloropicrin
Risk Characterization Document (RCD) (DPR 2012)
RCD – Exposure Assessment Document (Beauvais 2012)
RCD – OEHHA comments on 2011 draft RCD/EAD and DPR responses (OEHHA 2012)
Chloropicrin as a Toxic Air Contaminant (TAC) – Executive Summary (DPR 2010a)
TAC – Part A (Exposure Assessment) (DPR 2010b)
TAC – Part B (Human Health Risk Assessment) (DPR 2010c)
TAC – OEHHA Findings (Fan and Marty 2009)
TAC – Scientific Review Panel Findings (SRP 2010)
TAC – Decision by DPR Director (Warmerdam 2010)

Methyl Iodide
Risk Characterization Document (2010) Volume I – Health Risk Assessment (DPR 2010d)
Appendices to Volume I (DPR 2010e)
Volume II – Exposure Assessment (DPR 2010f)
Volume III – Environmental Fate (DPR 2010g)
Volume IV (Part 1) – Responses to External Peer Review Panel (DPR 2010h)
Volume IV (Part 2) – Responses to Public Comments (DPR 2010i)

Carbaryl
Dietary Risk Characterization Document (DPR 2010j)

EPA Guidance Documents

DPR also noted that it uses the following EPA guidance documents. The committee did not review these documents.

Guidelines for Mutagenicity Risk Assessment (EPA 1986)
Guidelines for Developmental Toxicity Risk Assessment (EPA 1991)
Guidelines for Reproductive Toxicity Risk Assessment (EPA 1996)
Guidelines for Neurotoxicity Risk Assessment (EPA 1998)
Review of the Reference Dose and Reference Concentration Processes (EPA 2002)
Guidelines for Carcinogen Risk Assessment (EPA 2005)

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Appendix C

Technical Recommendations for Department of Pesticide Regulation Risk Assessments

This appendix highlights specific technical observations made by the committee in its review of the Department of Pesticide Regulation (DPR) risk-assessment guidance and the risk-characterization documents on carbaryl, chloropicrin, and methyl iodide. These observations led to the conceptual recommendations made in the body of this report. The committee here offers recommendations on specific aspects of the performance of DPR's risk assessments.

DEFINITION OF ADVERSE EFFECTS

Sound scientific practice for hazard identification involves a determination of whether an observed effect is adverse. The US Environmental Protection Agency (EPA) defines an adverse effect as "a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or that reduces an organism's ability to respond to an additional environmental challenge" (EPA 2014a). Defining adverse effects is acknowledged to be difficult (e.g., see Lewis et al. 2002): not all effects are adverse, some effects might be adaptive responses, and others are precursors to adverse effects. Defining adverse effects is important as regulatory agencies begin to incorporate suggestions from the National Research Council Report *Toxicity Testing in the 21st Century: A Vision and a Strategy* (NRC 2007) into risk assessments in that precursor effects determined in in vitro studies may be suitable end points for risk assessments.

DPR's risk-characterization documents refer to no-observed-adverse-effect levels (NOAELs) and no-observed-effect levels (NOELs), both of which seem to be considered relevant to hazard identification. However, it is unclear how DPR defines an adverse effect on which those levels are based. The committee recommends that DPR clarify its definition and the criteria that it uses to make determinations. Consideration should be given to the technical support document developed by the Office of Environmental Health Hazard Assessment (OEHHA) for deriving noncancer reference exposure levels (OEHHA 2008) and to the work of EPA (2002) and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC 2002; Lewis et al. 2002). Consideration should also be given to establishing guidance or using existing guidance (e.g., ATSDR 2007; OEHHA 2008) on categorizing effects as mild, moderate, or severe.

ROUTE-TO-ROUTE EXTRAPOLATION

Extrapolation of dose–response data from one route of exposure to another is accompanied by uncertainty, which should be minimized as much as the data and methods allow. The major factors contributing to the uncertainty are the relevance of portal-of-entry effects in the lung or gastrointestinal tract to the extrapolated route of exposure, the liver first-pass effects that follow oral dosing that would result in an expectation of adverse effects different from those due to inhalation exposure, and the accuracy of dosimetry adjustments to normalize the internal dose and

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biologically effective dose achieved by the compared exposure routes (pharmacokinetic differences). If either a first-pass effect or portal-of-entry effect is present, route-to-route extrapolation is not recommended by EPA for derivation of health values (EPA 1994). Typically, EPA does not perform such extrapolations for fumigant risk assessments when adequate inhalation data are available but prefers to use an inhalation-specific approach that estimates a human-equivalent concentration.

Route-to-route extrapolation may be performed when a chemical's mode of action has been characterized, the relevant dose metric has been identified (for example, parent chemical or metabolite), and a physiologically based pharmacokinetic (PBPK) model or an optimal inhalation model is available. If such models are not available, route-to-route extrapolation should be performed only when defensible (as discussed above). The committee recommends that DPR acknowledge the uncertainty and provide guidance on when a route-to-route extrapolation is defensible. A pertinent resource is OEHHA's draft update of risk-assessment guidelines for its Air Toxics Hot Spots Program (OEHHA 2014). If applicable to DPR's risk-assessment practices, relevant guidance could be adopted and would help to promote consistency between the groups.

In its review of DPR's risk-characterization documents on fumigants, the committee noted that DPR estimates doses of active ingredients (AIs) from inhalation studies by using a body-burden approach, and it was unclear why such estimation was necessary. For example, in the carcinogenic assessment of chloropicrin (DPR 2012), an inhalation study of mice that developed lung adenomas and carcinomas (portal-of-entry effects) after chronic exposure to chloropicrin was available. DPR adjusted the air concentrations (in parts per million) from that study into doses (milligrams per kilogram per day) and then converted the doses to human equivalents by multiplying by an interspecies scaling factor applicable for an oral route of exposure (body weight to the ¾ power). The resulting dose was converted back to an air concentration. Because chloropicrin has an adequate inhalation study in mice and produces portal-of-entry effects, route-to-route extrapolation is unnecessary. DPR should have used inhalation-specific dosimetric adjustments. Guidance on performing such adjustments is available, as is guidance on when route-to-route extrapolation is scientifically defensible (see EPA 1994).

BENCHMARK-DOSE MODELING

DPR uses benchmark-dose (BMD) modeling in its dose–response assessments of AIs when only a lowest-observed-adverse-effect level has been identified in a study (DPR 2004a,b). The committee supports BMD modeling and recommends that DPR expand its use of it to all cases in which the dose–response data are amenable to modeling, even when a NOEL or NOAEL has been identified. EPA has more recent guidance on BMD modeling (EPA 2012a), which DPR should review and use to update its BMD guidance documents, if needed, to reflect the latest scientific recommendations. The committee observed that the response level chosen for the BMD and BMDL varies from case to case. For example, 1%, 2.5%, 5%, and 10% response levels were used for chloropicrin (DPR 2012). That can lead to inconsistency in end-point comparisons between different critical effects. In addition, caution should be used in extrapolating far below the observed range of data because it introduces uncertainty into the assessment. Expanding the use of BMD methods and defining response levels consistently will allow DPR to be consistent with dose–response practices of OEHHA (2008) and EPA (2012a).

CHEMICAL-SPECIFIC ADJUSTMENT FACTORS

The committee recommends that DPR consider the derivation of chemical-specific adjustment factors if chemical-specific data are available. The International Programme on Chemical Safety has guidance on the data needed to develop chemical-specific adjustment factors to account for interspecies differences and human variability in toxicokinetics and toxicodynamics

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(IPCS 2001, 2005). EPA (2014b) guidance on data-derived extrapolation factors provides a fairly similar approach.

ANIMAL-TO-HUMAN DOSIMETRIC ADJUSTMENTS

Animal-to-human dosimetric adjustments may be performed when a chemical's mode of action has been characterized, the relevant dose metric has been identified (for example, parent chemical or metabolite), and a PBPK model or an optimal inhalation model is available. If models are not available, default procedures are typically used. DPR and EPA appear to differ in how they perform default animal-to-human dosimetric adjustments. For example, DPR (2011) adjustments appear to be based on different breathing rates for different life stages to estimate inhalation risk to humans whereas EPA's calculations depend on default animal-to-human dosimetric adjustments (EPA 1994). DPR does not use EPA's default adjustments for extrarespiratory effects (systemic effects), because of the uncertainty associated with the lack of chemical-specific data on human and animal blood-gas ratios (DPR 2011). The committee recommends that DPR review EPA (2012b) recommendations for animal-to-human dosimetric adjustments for adverse respiratory effects in the extrathoracic, tracheobronchial, and pulmonary regions for gases and vapors. The dosimetric adjustments are default procedures and are considered appropriate on the basis of PBPK inhalation modeling and measured data for various chemicals. EPA also judges that the adjustments are protective of children in the great majority of cases. Specific exceptions are discussed (see EPA 2012b).

Attachment 1 of DPR (2011) focused on inhaled gases and did not address dosimetric adjustment factors for inhaled particles or aerosols. For inhaled particles and aerosols, the committee recommends that DPR consider EPA (1994) procedures to determine the appropriate dosimetric adjustment factor except for rat inhalation studies. For rats, the multiple-path particle dosimetry model, version 2, for performing dosimetric adjustments (CIIT 2004) is generally used.

The committee notes that DPR sometimes uses PBPK models to conduct animal-to-human dosimetric adjustments. Other types of optimal inhalation-dosimetry models that DPR could use are available. Hanna et al. (2001) describe differences between basic inhalation-dosimetry models and provide some guidance on factors to consider in choosing model structures.

DEFAULT ANIMAL-TO-HUMAN DOSIMETRIC ADJUSTMENTS THAT AFFECT THE VALUE OF THE INTERSPECIES UNCERTAINTY FACTOR

The DPR (2011) guidance document for default uncertainty factors acknowledges some inconsistency in how interspecies extrapolations are performed by DPR, OEHHA, and EPA. All groups consider that the interspecies uncertainty factor consists of a toxicokinetic portion ($10^{0.5}$) and a toxicodynamic portion ($10^{0.5}$). EPA (1994) reference-concentration methods recommend that for the inhalation route of exposure, when the animal concentration can be adjusted by a dosimetric adjustment factor (if data are available) to a human-equivalent concentration, the pharmacokinetic portion ($10^{0.5}$) be reduced to 1 because toxicokinetic differences between animals and humans have been taken into consideration. OEHHA (2008) recommends that when such an adjustment is performed, the toxicokinetic portion of the uncertainty factor be reduced to 2, rather than 1, to reflect remaining uncertainty about toxicokinetics due to metabolism and excretion. DPR's guidance does not appear to allow estimation of a human-equivalent concentration and presents default values of $10^{0.5}$ for both the pharmacokinetic and pharmacodynamic portions of the uncertainty factor. The committee recommends that DPR's guidance be updated to allow estimation of human-equivalent concentrations from animal data and relevant adjustment of the pharmacokinetic portion of the uncertainty factor applied for interspecies differences.

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Appendix D

Pesticide Toxicity Estimates of the Department of Pesticide Regulation and the US Environmental Protection Agency Used to Generate Bottom Histogram of Figure 3-3

Toxicity Estimates from Pesticide Assessments Completed by DPR in 2004–2014 and from EPA

	Toxicity Estimates[a]		
Pesticide	DPR NOEL, mg/kg-day	EPA NOEL, mg/kg-day	EPA:DPR Ratio[b]
2010–2014			
SIMAZINE (2014)			
Acute, dietary	5	30	6
Acute, nondietary	5	6.25	1.3
Subchronic	0.56	1.18	2.1
Chronic	0.52	1.18	2.3
Carcinogen (threshold)	2.9	No	DPR higher potency
PHOSPHINE (2013)			
Acute, inhalation	5 ppm	5 ppm	1
Subchronic, inhalation	1	3	3
Chronic, inhalation	1	3	3
Carcinogen	No	No	Same
CARBARYL (2012)			
Acute, oral	1	1.1	1.1
Acute, dermal	20	86	4.3
Acute, inhalation	1	1.1	1.1
Carcinogen (Q*)	9.72×10^{-3}	8.75×10^{-4}	DPR 11× higher potency
PROPARGITE (2012)			
Acute, oral	2	8	4
Acute, inhalation	5	5	1
Subchronic, dermal	1	4	4
Subchronic, inhalation	0.5	5	10
Chronic, oral	3.8	4	1.1
Carcinogen (Q*)	2.6×10^{-2}	3.3×10^{-2}	Same (0.5–2.0)
METHYL PARATHION (2010)			
Acute, dermal	0.025	0.1	4
Subchronic, inhalation	0.03	0.11	3.7
Subchronic, dermal	0.03	0.1	3.3
Chronic	0.02	0.02	1
Carcinogen	No	No	Same

(Continued)

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Toxicity Estimates from Pesticide Assessments Completed by DPR in 2004–2014 and from EPA *(continued)*

2004–2009			
ENDOSULFAN (2008)			
Acute, oral	0.7	1.5	2.1
Acute, dermal	0.7	1.25	1.8
Acute, inhalation	0.194	0.2	1
Subchronic, dermal	1.18	1.25	1.1
Subchronic, inhalation	0.194	0.2	1
Chronic, oral	0.57	0.6	1
Carcinogen	No	No	Same
METHIDATHION (2007)			
Acute, oral	0.18	0.2	1.1
Acute, dermal	0.18	20	111
Subchronic	0.18	0.2	1.1
Chronic	0.15	0.15	1
Carcinogen	0.53	No	DPR higher potency
CARBOFURAN (2006)			
Acute	0.01	0.08	8
Subchronic	0.1	0.08	0.8
Chronic	0.1	0.025 (300)	0.083
Carcinogen	No	No	Same
METAM SODIUM (2004)			
Acute	1	4.22	4.2
Subchronic	0.2	0.1	0.5
Chronic	0.1	0.1	1
Carcinogen (Q*)	1.85×10^{-1}	1.98×10^{-1}	Same (0.5–2.0)
AZINPHOSMETHYL (2004)			
Acute, oral/dermal	0.75 (10)	1	0.13
Subchronic, oral	0.25 (30)	0.149	0.18
Chronic	0.15 (30)	0.149	0.3
Carcinogen (Q*)	No	No	Same
METHAMIDIPHOS (2001/2007)			
Acute, oral	0.3	0.3 (300)	0.33
Acute, dermal	3	0.75	0.25
Subchronic, dermal	0.75	0.75	1
Chronic, oral	0.02	0.03 (300)	0.5
Carcinogen (Q*)	No	No	Same

[a]Values obtained from G. Patterson, California Department of Pesticide Regulation, personal communication, July 1, 2014. Target MOEs were 100 except where noted in parentheses.
[b]The ratio includes allowance for MOEs that differ from 100 (NOEL/MOE [EPA] ÷ NOEL/MOE [DPR]).
Abbreviations: DPR, Department of Pesticide Regulation; EPA, US Environmental Protection Agency; MOE, margin of exposure; NOEL, no-observed-effect level; Q*, cancer potency factor.

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