Refinements to the Methods for Developing Spacecraft Exposure Guidelines

DETAILS

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Committee on Spacecraft Exposure Guidelines

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

The National Aeronautics and Space Administration (NASA) has an active interest in the environmental conditions associated with living and working in spacecraft and identifying hazards that might adversely affect the health and well-being of crew members. Despite advanced engineering in controlling the spacecraft environment, some air and water contamination is inevitable. Several hundred chemicals are likely to be found in the closed environment of the spacecraft, and as the frequency, complexity, and duration of human spaceflight increase, identifying and understanding significant health hazards will become more complicated and more critical for the success of the missions.

The National Academies of Sciences, Engineering, and Medicine have a long history of assisting NASA with developing spacecraft maximum allowable concentrations (SMACs) for air contaminants and spacecraft water exposure guidelines (SWEGs). The methods for establishing those exposure guidelines were issued in 1992 and 2000, respectively. Because there have been new developments in risk assessment practices and emerging areas of toxicology research, NASA requested that the Academies update the methods for deriving SMACs and SWEGs and subsequently review revisions to existing guidelines or proposed guidelines for additional chemicals.

In response to this request, the Academies convened the Committee on Spacecraft Exposure Guidelines (see Appendix A for biographical information on the members). In this report, the committee outlines current practices in risk assessment and provides recommendations for incorporating refinements into developing SMACs and SWEGs. Additional advancements and more refined practices will be made during the years it will take NASA to develop SMACs and SWEGs, so it is anticipated that further refinements could be made on an ongoing basis.

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise. 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 this

report: Victoria Cassano, Performance Medicine Consulting; Rogene Henderson, Lovelace Respiratory Research Institute (retired); John Morris, University of Connecticut; Bruce Naumann, Merck & Company; John O'Donoghue, independent consultant; and R. Leonard Vance, Virginia Commonwealth University.

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 the review coordinator, James Lockey, University of Cincinnati, who was 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 committee and the institution.

The committee gratefully acknowledges the following for their presentations to the committee during open sessions: Torin McCoy, Valerie Ryder, and John James (retired) from NASA; Hector Garcia and Raghupathy Ramanathan from Wyle Science, Technology, and Engineering Group; and Pamela Dalton from Monell Chemical Senses Center.

The committee is grateful for the assistance of the Academies staff in preparing this 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 the effort are Elizabeth Boyle, program officer; James Reisa, director of the Board on Environmental Studies and Toxicology; and Tamara Dawson, program associate.

I especially thank the members of the committee for their efforts throughout the development of this report.

Edward C. Bishop, *Chair*
Committee on Spacecraft Exposure Guidelines

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Refinements to the Methods for Developing SPACECRAFT EXPOSURE GUIDELINES

Summary

Human spaceflight is inherently risky, with numerous potential hazards posed at each phase of a mission. Potential health risks during spaceflights include short-term health consequences from being in microgravity, as well as long-term health consequences that arise, or continue, months or years after a flight. Additional health considerations are risks posed by exposure to environmental contaminants onboard spacecraft. Because the International Space Station and spacecraft are closed environments that require recirculation of air and water supplies, some contamination of the air and water will occur. Even with onboard air and water purification systems, chemicals will accumulate in the air and water as they recirculate or are recycled onboard. Therefore, it is necessary for the National Aeronautics and Space Administration (NASA) to identify hazardous contaminants and determine exposure levels that are not expected to pose a health risk to astronauts.

NASA uses spacecraft maximum allowable concentrations (SMACs) and spacecraft water exposure guidelines (SWEGs) to provide guidance on acceptable exposures to air and water contaminants during normal operations and emergency situations. Short-term SMACs and SWEGs are concentrations intended to prevent irreversible harm and degradation in crew performance during rare emergency conditions lasting for periods up to 24 hours. Longer-term SMACs and SWEGs are intended to prevent adverse health effects (either immediate or delayed) and degradation in crew performance that could result from continuous exposure in closed spacecraft for as long as 1,000 days.

The National Academies of Sciences, Engineering, and Medicine have a long history of supporting NASA in the setting of chemical exposure guidelines. Methods for developing SMACs and SWEGs were established in 1992 and 2000, respectively, and exposure guidelines were developed continuously until 2008. In 2015, NASA requested that the Academies resume its assistance to the agency by updating the methods for establishing SMACs and SWEGs. In response to the request, the Academies convened the Committee on Spacecraft Exposure Guidelines, which held two public meetings to get background on the original methods and to gather other relevant information. The committee has focused on identifying refinements that could be made to NASA's existing procedures that would bring them more in line with advances that have been made in risk assessment. NASA will use the updated methods to reevaluate some of the existing exposure

guidelines and to develop SMACs and SWEGs for new chemicals, and the committee will subsequently review the proposed guidelines to ensure that they are derived in accordance with current risk assessment practices.

REFINING THE PROCESS OF DEVELOPING EXPOSURE GUIDELINES

NASA's approach to deriving SMACs and SWEGs has followed established risk-assessment practices and will remain largely the same as in the past, but a number of refinements to the process have since been developed to help improve the basis of the exposure guidelines. To establish exposure guidelines, NASA conducts hazard assessments on individual contaminants. The hazard assessment process includes evaluating the scientific literature over a broad range of information, including the physical and chemical characteristics of the contaminant, in vitro toxicity studies, toxicokinetic studies, animal toxicity studies conducted over a range of exposure durations, carcinogenicity bioassays, human clinical and epidemiologic studies, and mechanistic studies. In recent years, other federal agencies have begun implementing procedures for better documenting how they conduct literature-based evaluations, so that other stakeholders and the public can understand and replicate them. The procedures typically include documenting the literature search strategies, specifying the criteria that are used to select studies, and describing how different lines of evidence were integrated to draw conclusions about critical health end points.

Recommendations:

> *NASA should provide better documentation of its strategy for conducting literature searches and the basis for selecting studies for inclusion in the chemical assessment. For the literature searches, a template should be created to describe the search approach to ensure that relevant information is captured. At a minimum, NASA should specify the databases and sources that were searched, describe the search strategies for each database and source searched, and specify the dates of each search and the publication dates included.*

The starting point for calculating SMACs and SWEGs is the dose or exposure concentration associated with a critical effect. Ideally, the point of departure is obtained from human data, but may also be obtained from a well-conducted animal study. When sufficient dose-response data are available, NASA uses quantitative approaches (e.g., benchmark dose modeling) to estimate the dose or concentration associated with a specified response incidence (e.g., 1-10%). Points of departure can also be derived from physiologically based pharmacokinetic models, which can be designed to estimate appropriate dose metrics, such as estimates of human equivalent doses from animal data, to address route-to-route extrapolations,

and to facilitate high-to-low dose extrapolations. In the absence of dose-response data, a no-observed-adverse-effect level or a lowest-observed-adverse-effect level is used. The point of departure is subsequently adjusted by uncertainty factors to account for uncertainties associated with the data.

For noncancer end points, NASA has considered the traditional set of uncertainty factors used in risk assessment, as well as "spaceflight factors" to account for additional uncertainties associated with the physical, physiological, and psychological changes that occur in microgravity. The six spaceflight factors that have been used by NASA are for microgravity effects on bone mineral density, renal stone formation, the cardiovascular system, red-blood-cell formation, immune response, and organoleptic considerations. Such spaceflight factors are applied when the effects of a chemical could be exacerbated by one of these conditions. Data should be used whenever possible to select the magnitude of the uncertainty or spaceflight factor or to eliminate the need for it, including data on similar chemicals, toxicokinetic and toxicodynamic data, or other data that allow quantification of differences or variability.

The committee observed that the direct and indirect effects of microgravity on the liver do not appear to have been routinely considered by NASA in the past. The stresses of spaceflight may affect the normal function of the liver as well as potentially increase its susceptibility to chemical injury, depending on a specific chemical's mode of toxic action. Thus, it will be prudent to consider a spaceflight factor for hepatic effects in updating or establishing SMACs or SWEGs.

Recommendations:

- *NASA should ensure that key decisions made in deriving SMACs and SWEGs are explained and justified. Examples of key decision points are the selection of the point of departure, determining the magnitude of the uncertainty and spaceflight factors, and extrapolation procedures.*
- *An additional spaceflight factor for susceptibility or exacerbation of effects on liver function should be added to the special spaceflight considerations used in deriving SMACs and SWEGs.*
- *The values of the uncertainty and spaceflight factors should be selected on the basis of chemical-specific data, to the extent possible. The factors should be considered in context with each other to avoid making duplicative adjustments for the same uncertainty.*

SELECTING AND PRIORITIZING CHEMICALS

The options for choosing candidate chemicals for risk assessment remain the same as previously established. One choice is subjective in which selections are made on the basis of informed expert judgment. The second approach provides a slightly more formal approach, in which parameters for making the decision are specified but their weights and interrelationships are not. The third ap-

proach is more formulaic and involves specifying and quantifying the elements that are considered and using a weighting system for ranking contaminants. Overall, the committee found that these and other ranking schemes all involve a mix of data and to some degree expert judgment. The main differences are the specific mix of parameters considered and the extent to which explicit or implicit judgments come together to produce reliable results. The committee concluded that the output of most prioritization schemes is so uncertain that they are only useful in making preliminary screening assessments or classifications and should not be used for sorting contaminants in a specific order.

Recommendation:

> *The committee endorses NASA's use of a combination of approaches to select chemicals for risk assessment. The process should be described to support the selection process.*

1

Introduction

Human spaceflight is inherently risky, with numerous potential hazards posed at each phase of a mission, including launch, inflight during the mission, and landing. Potential health risks during spaceflights include short-term health consequences from being in microgravity (e.g., nausea, blurred vision), as well as long-term health consequences that arise, or continue, months or years after a flight (e.g., radiation-induced cancers, loss of bone mass). Additional health considerations are risks posed by exposure to environmental contaminants onboard spacecraft. Because the International Space Station and spacecraft are closed environments, some contamination of the air and water will occur. Even with onboard air and water purification systems, chemicals will accumulate in the air and water supplies as they recirculate or are recycled onboard. Therefore, it is necessary for the National Aeronautics and Space Administration (NASA) to identify hazardous contaminants and determine exposure levels that are not expected to pose a health risk to astronauts.

The National Academies of Sciences, Engineering, and Medicine have a long history of supporting NASA in the setting of chemical exposure guidelines. This effort began in 1968 with the National Research Council (NRC) Space Science Board's Panel on Air Standards for Manned Space Flight, which provided guidance on provisional guidelines for 39 chemicals (NRC 1968). In 1972, NASA requested that another panel be formed to review those exposure guidelines and to set new guidelines where appropriate. The new guidelines were necessary to provide engineering benchmarks to guide the development of advanced life-support systems for long-duration space missions. The Panel on Air Quality in Manned Spacecraft established 1-hour, 90-day, and 6-month exposure guidelines for 52 compounds (NRC 1972).

In 1990, the NRC and NASA resumed the effort to set chemical exposure guidelines in anticipation of launching a manned space station. Because several hundred atmospheric chemicals would likely be found in the complex, closed environment of the space station, an understanding of how contaminants are generated and the concentrations that are likely to pose a health hazard to crew members was needed to design the trace contaminant control system. An NRC committee developed methods for determining spacecraft maximum allowable concentrations (SMACs) for airborne contaminants, which included guidance on

the types of toxicologic information to consider and methods for calculating appropriate exposure guidelines (NRC 1992). NASA subsequently used those methods to derive SMACs for numerous compounds (see Table 1-1), and its documents were reviewed by the committee to ensure that they had been developed in accordance with the methods and were scientifically justified. SMACs are defined as the maximum concentration of airborne substances (e.g., gas, vapor, or aerosol) that will not cause adverse health effects, significant discomfort, or degradation in crew performance. SMACs are classified into short-term (1 or 24 hours) and longer-term (7, 30, 180, and 1,000 days) durations. The 1- and 24-hour SMACs are to be used in emergency situations, such as accidental spills or fire. Temporary discomfort is permissible as long as there is no effect on the ability to respond to the emergency. The longer-term SMACs are intended to avoid adverse health effects (either immediate or delayed) and to avoid degradation in performance of crew after continuous exposure for as long as 1,000 days. The need for a 1,000-day SMAC was introduced by NASA in the early 2000s. Five volumes of SMAC documents and guidelines were published between 1994 and 2008 (NRC 1994, 1996a, 1996b, 2000a, 2008a).

In 2000, a similar procedure was used to begin establishing spacecraft water exposure guidelines (SWEGs). To provide a space crew with an adequate water supply, it is necessary to recycle spacecraft wastewater during long-duration flights. Water can be recovered onboard from sources such as humidity condensate, used hygiene water, and urine, and controls are needed to prevent contaminants from reaching concentrations that might pose a health risk to astronauts. Thus, at the request of NASA, an updated set of methods for establishing exposure guidelines was developed, focusing on special considerations for water contaminants (NRC 2000b). Like SMACs, SWEGs are set for short-term (1 day) and longer-term (10, 100, and 1,000 days) durations. The 1-day SWEG is a concentration of a substance in water that is judged to be acceptable for the performance of specific tasks during rare emergency conditions lasting for periods up to 24 hours. The 1-day SWEG is intended to prevent irreversible harm and degradation in crew performance. Temporary discomfort is permissible as long as there is no effect on judgment, performance, or ability to respond to an emergency. Longer-term SWEGs are intended to prevent adverse health effects (either immediate or delayed) and degradation in crew performance that could result from continuous exposure in closed spacecraft for as long as 1,000 days. In contrast with the 1-day SWEG, longer-term SWEGs are intended to provide guidance for exposure under what is expected to be normal operating conditions in spacecraft, and includes consideration of the taste and smell of the water. The exposure durations of the guidelines for water differ from those of air because exposure to water is more intermittent than is exposure to air and because it is possible to refrain from drinking or using contaminated water for short periods in an emergency. NASA developed SWEGs for numerous compounds (see Table 1-1), which were reviewed by the committee and published in three volumes between 2000 and 2008 (NRC 2004, 2007, 2008b).

TABLE 1-1 Chemicals with SMAC or SWEG Guidelines

Chemical	SMAC	SWEG
Acetaldehyde	NRC (1994)	–
Acetone	NRC (2000a)	NRC (2007)
Acrolein	NRC (2008a)	–
C2-C9 Aliphatic alkanes	NRC (2008a)	–
Alkylamines (di)	–	NRC (2007)
Alkylamines (mono)	–	NRC (2007)
Alkylamines (tri)	–	NRC (2007)
C3-C8 Aliphatic saturated aldehydes	NRC (2008a)	–
Ammonia	NRC (2008a)	NRC (2007)
Antimony (soluble salts)	–	NRC (2008b)
Barium (salts), soluble	–	NRC (2007)
Benzene	NRC (2008a)	NRC (2008b)
Bromotrifluoromethane	NRC (1996b)	–
1-Butanol	NRC (2008a)	–
tert-Butanol	NRC (1996b)	–
Cadmium (salts), soluble	–	NRC (2007)
Caprolactum	–	NRC (2007)
Carbon dioxide	NRC (2008a)	–
Carbon monoxide	NRC (2008a)	–
Chloroform	NRC (2000a)	NRC (2004)
Decamethylcyclopentasiloxane	NRC (2000a)	–
Diacetone alcohol	NRC (1996b)	–
Dichloroacetylene	NRC (1996b)	–
1,2-Dichloroethane	NRC (2008a)	–
Di(2-ethylhexyl) phthalate	–	NRC (2004)
Di-*n*-butyl phthalate	–	NRC (2004)
Dichloromethane	–	NRC (2004)
Dimethylsilanediol	–	Ramanathan et al. (2012)
Ethanol	NRC (2008a)	–
2-Ethoxyethanol	NRC (1996a)	–
Ethylbenzene	NRC (1996b)	–
Ethylene glycol	NRC (1996b)	NRC (2008b)
Formaldehyde	NRC (2008a)	NRC (2007)
Formate	–	NRC (2007)
Freon 11	NRC (2000a)	–
Freon 113	NRC (1994)	–
Freon 12	NRC (2000a)	–
Freon 21	NRC (2000a)	–
Freon 22	NRC (2000a)	–
Furan	NRC (2000a)	–
Glutaraldehyde	NRC (1996b)	–
Hexamethylcyclotrisiloxane	NRC (2000a)	–

(Continued)

TABLE 1-1 Continued

Chemical	SMAC	SWEG
Hydrazine	NRC (1996a)	–
Hydrazine	NRC (1996a)	–
Hydrogen	NRC (1994)	–
Hydrogen chloride	NRC (2000a)	–
Hydrogen cyanide	NRC (2000a)	–
Indole	NRC (1996a)	–
Isoprene	NRC (2000a)	–
Lead	–	Garcia et al. (2014)
Limonene	NRC (2008a)	–
Manganese (salts), soluble	–	NRC (2007)
2-Mercaptobenzothiazole	–	NRC (2004)
Mercury	NRC (1996a)	–
Methane	NRC (1994)	–
Methanol	NRC (2008a)	NRC (2008b)
Methyl ethyl ketone	NRC (1996a)	NRC (2008b)
Methyl hydrazine	NRC (2000a)	–
4-Methyl-2-pentanone	NRC (2000a)	–
Methylene chloride	NRC (2008a)	–
Nickel	–	NRC (2004)
Nitromethane	NRC (1996a)	–
Octamethylcyclotetrasiloxane	NRC (2000a)	–
Octamethyltrisiloxane	NRC (1994); Meyers et al. (2013)	–
Perfluoropropane	NRC (2000a)	–
Phenol	–	NRC (2004)
n-Phenyl-beta-naphthylamine	–	NRC (2004)
2-Propanol	NRC (1996a)	–
Propylene glycol	NRC (2008a)	NRC (2008b)
Siloxanes, linear (short chain)	Meyers et al. (2013)	–
Silver	–	NRC (2004)
Toluene	NRC (2008a)	
Total organic carbon	–	NRC (2007)
Trichloroethylene	NRC (1996b)	–
Trimethylsilanol	NRC (2008a)	–
Unsymmetrical dimethylhydrazine	NRC (2008a)	–
Vinyl chloride	NRC (1994)	–
Xylene	NRC (2008a)	–
Zinc, soluble compounds	–	NRC (2007)

SMACs and SWEGs are established for use by the US space program, so they are designed for astronauts who have been medically screened and have undergone rigorous testing. Thus, the guidelines are based on the understanding that the astronaut population consists of healthy adults with no preexisting medical conditions (e.g., asthma).

THE PROCESS OF DEVELOPING AND REVIEWING SMACS AND SWEGS

The following process has been used by NASA and previous NRC committees to establish SMACs and SWEGs. NASA identifies the air and water contaminants of concern to its spaceflight program and determines which chemicals should undergo a comprehensive assessment to establish SMACs or SWEGs. NASA staff and contractors conduct literature-based toxicologic assessments of the selected chemicals, which involve the performance of literature searches, summarization of the literature, and selection of relevant studies from which to derive exposure guidelines. Acceptable exposure concentrations are calculated for health end points of concern, and exposure guidelines are proposed. NASA's assessments are presented at NRC committee meetings, and the committee's review and recommendations are documented in interim reports. If substantive changes are required that could affect the proposed SMACs or SWEGs, the committee reviews these changes at subsequent meetings. After the committee has approved a SMAC or SWEG document, it is published. The same process will be used for updating SMACs and SWEGs and for establishing exposure values for new chemicals.

ADVANCEMENTS IN RISK ASSESSMENT

Improved approaches for performing literature-based toxicologic assessments to support risk assessment have been outlined in several NRC reports (e.g., NRC 2009, 2011, 2014). These improvements are directed at programs of the US Environmental Protection Agency for the purpose of ensuring public health protection, so they have been developed for purposes outside of NASA's purview and many aspects are not appropriate for setting SMACs and SWEGs (e.g., protecting the health of children). However, certain themes are relevant to NASA, such as the need for transparency and the importance of incorporating biologically-based, mode-of-action, and quantitative approaches into assessments as much as possible. The use of quantitative approaches over qualitative assessments is encouraged when estimating exposure guidelines, as mathematical models and statistical analyses can now be used at various steps of the risk assessment process, such as analyzing dose-response data to estimate doses associated with a low level of response, to quantify species differences, or to pool data from multiple studies. Transparency is an overarching aspect of performing toxicologic assessments, because it is critical that an assessment is understandable, that enough information is presented so that it would be possible to reproduce the assessment, that modeling approaches and assumptions are supported, and that departures from default approaches are adequately justified.

STATEMENT OF TASK

In light of updated approaches to conducting toxicologic assessments, NASA requested that an ad hoc committee be convened to assist the agency with developing spacecraft exposure guidelines for individual air and water contaminants. The committee will build on and update the Academies' previous work for NASA on developing SMACs for air contaminants and SWEGs for water contaminants. The committee was asked to perform the following tasks:

- Update the guidelines and methods for developing SMACs and SWEGs.
- Assist NASA with identifying chemicals that need updated SMACs or SWEGs and new chemicals for which SMACs or SWEGs should be developed.
- Review the scientific basis of NASA's proposed SMACs and SWEGs and ensure they have been developed in accordance with the updated guidelines.

This report addresses the first two tasks of updating the guidelines and methods for developing exposure guidelines for use on spacecraft and outlining procedures that can be used for choosing chemicals to evaluate. NASA will use the updated methods to reevaluate some of the existing exposure values and to develop SMACs and SWEGs for new chemicals, and the committee will subsequently review the proposed exposure guidelines to ensure that they were derived in accordance with current risk assessment practices. The updated SMACs and SWEGs will be published in future reports.

APPROACH TO THE STUDY

The Academies convened the Committee on Spacecraft Exposure Guidelines in 2015. Members of the committee have expertise in general toxicology, inhalation toxicology, neurotoxicology, toxicokinetics, mechanisms, industrial hygiene, occupational health, and risk assessment. Two public meetings were held to familiarize the committee members with the original methods used by NASA to develop SMACs and SWEGs, and to gather other information relevant to updating the assessment methods. The committee focused on identifying refinements that could be made to NASA's existing procedures that would bring them more in line with advances that have been made in risk assessment.

ORGANIZATION OF THE REPORT

This report is organized into the Introduction, two additional chapters, and two appendixes. Chapter 2 outlines the process of deriving SMACs and SWEGs and identifies refinements in risk assessment practices that NASA should begin to use in updating its existing guidelines and in deriving guidelines for additional

chemicals. Chapter 3 reviews approaches to selecting and ranking contaminants for assessment. Appendix A provides biographical information on the committee members, and Appendix B provides examples of report outlines that might be used for organizing future SMAC and SWEG documents.

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2

Derivation of SMACs and SWEGs

The methods for developing spacecraft maximum allowable concentrations (SMACs) and spacecraft water exposure guidelines (SWEGs) are similar to those used to establish exposure guidelines in occupational settings and for the general public. The approach involves evaluating the scientific literature on a specific chemical, identifying studies relevant to the desired exposure guideline, determining critical effects, selecting a point of departure (dose or concentration used as a starting point for calculating an exposure guideline) for each critical effect, making exposure conversions, and accounting for uncertainties and variability (including those uniquely associated with spaceflight). Refinements have been made to elements of this process since the previous guidance on establishing SMACs (NRC 1992) and SWEGs (NRC 2000), but the overall process remains the same. (For background information on risk assessment practices and proposed improvements, see NRC [2009, 2014] and the 2015 special issues of *The Journal of Occupational and Environmental Hygiene [Vol. 12, Supplement 1]*). The sections below highlight the refinements to the National Aeronautics and Space Administration's (NASA's) existing guidance that should be implemented in updating SMACs or SWEGs or in establishing guidelines for new chemicals. With this approach, both the scientific credibility of the exposure guidelines and the reduction in risk to the spacecraft crew will be ensured as chemicals are reevaluated and new exposure guidelines are developed.

EVIDENCE IDENTIFICATION AND INTEGRATION

The first step in developing SMACs and SWEGs is the conduct of a comprehensive literature search of both published and unpublished data from animal and human studies. Recent guidance on performing toxicologic assessments has called for more transparent documentation of how literature searches are performed, and suggests that a template be created to describe the search approach to ensure that relevant information is captured (NRC 2014). Important elements to document are the databases and sources searched, the search strategies, the dates on which the searches were performed, and the publication dates included.

Systematic review methods that were established for conducting literature-based clinical evaluations (e.g., see IOM 2011) are now being adapted for the

purposes of evaluating environmental health data. The methods involve searching for evidence, addressing possible reporting biases, screening and selecting studies, documenting the search, and managing data. In 2015, the National Toxicology Program's Office of Health Assessment and Translation released guidance on the conduct of literature-based health assessments that formally incorporate systematic review and evidence integration methods (NTP 2015). Another group at the University of California, San Francisco, has also developed a method called the Navigation Guide to facilitate a systematic and transparent method of research synthesis (Woodruff and Sutton 2014). Although full adoption of such procedures are not recommended for NASA's purposes, elements of these procedures may be useful in guiding NASA on how to be more systematic in its approach to searching for studies, documenting the basis for how studies are selected, and demonstrating how evidence was integrated to make key decisions in deriving SMACs and SWEGs.

As outlined in previous guidance (NRC 1992, 2000), animal toxicity and human studies that are most relevant to the SMACs and SWEGs in terms of the route and duration of exposure should be reviewed, along with supporting mechanistic information to help interpret data. Data relevant to developing SMACs and SWEGs include effects on all the major organ systems, including developmental toxicity. Although pregnant astronauts are prohibited from missions, developmental effects could be of concern for a chemical with a long biological half-life and may be of concern in a subsequent pregnancy and should be reviewed in context of pharmacokinetic information. NASA should continue to periodically assess the epigenetic risks from long-term radiation, microgravity, or toxin exposure inherent from long-duration spaceflight. A growing body of evidence indicates that preconception parental exposure can have effects on genomic integrity of gametes, as well as epigenetic parental impacts (Lane et al. 2014). However, at present, the long-term effects of microgravity and specific toxins of concern on the gametes are unknown.

Supporting data for SMACs and SWEGs may include chemical-specific information regarding physical and chemical properties, degradation products, toxicokinetics, chemical interactions, mechanism information, biomarkers, organoleptic properties, and individual susceptibility, as well as data from in vitro studies. Quantitative structure-activity relationship models may also be used to augment sparse data on a specific chemical. More targeted literature searches may be required to identify relevant supporting information.

DERIVING SMACs AND SWEGs

Different approaches have been used to establish exposure guidelines on the basis of whether the end point of concern is a cancer or a noncancer effect. Typically, it has been assumed that carcinogens do not have a threshold of effect, so dose-response analyses have been designed to quantify the risks at low doses. In contrast, for noncancer end points, it is assumed that homeostatic and defense mechanisms lead to a dose threshold, below which adverse effects are

unlikely. Thus, the focus is on establishing exposure guidelines at which there is unlikely to be an appreciable risk of an adverse effect occurring. A 2009 National Research Council report recommended a transition from this dichotomous approach to a unified approach to dose-response assessment for cancer and noncancer end points, so that both are risk-based assessments (NRC 2009). Ideally the approach should strive to use a spectrum of data, provide a probabilistic characterization of risk, include explicit consideration of human heterogeneity, factor in background exposure and susceptibility, characterize uncertainties (probabilistic distributions rather than uncertainty factors), and address sensitive populations. Many of these aspects are implicit in the process used by NASA to derive exposure guidelines. Although some progress has been made in making this transition to a unified approach, more study and evaluation will be necessary before it becomes practical for NASA's purposes.

Cancer Risk Estimates

Since the previous SMAC and SWEG methods were published, additional guidance on performing cancer assessments has been issued by the US Environmental Protection Agency (EPA 2005). Use of mode-of-action information on potential carcinogens is a main focus of EPA's guidelines. Such information is used to evaluate the biological plausibility of in vivo observations, to understand potential susceptibilities, and to guide dose-response analyses. Estimation of carcinogenic risk involves fitting mathematical models to experimental data and extrapolating to predict risks at doses that are below the tested range. The point of departure is the dose or concentration associated with a degree of excess risk for cancer, which serves as the starting point for making extrapolations. In general, low-dose linear extrapolations are performed if a chemical (or a metabolite) is judged to be a carcinogen operating by a mutagenic mode of action (or information is lacking on mode of action), and nonlinear approaches are used for those that are not mutagenic and have sufficient data to support a nonlinear mode of action. For such chemicals, a margin-of-exposure analysis may be considered in which the point of departure for negligible risk is compared with the estimated exposure (EPA 2005). Benchmark dose (BMD) or benchmark concentration (BMC) methods are now the preferred means for estimating a dose or concentration associated with a low level of excess health risk, generally in the risk range of 1-10%. The point of departure is usually the lower bound on the dose that results in an excess risk of 10% based on fitting of a dose-response model to animal bioassay data (EPA 2012a). Extrapolation of the dose-response curve to lower doses is performed using a biologically based model, if adequate data are available. In the absence of such data, default approaches are used and are selected on the basis of whether mode-of-action information is available for making a judgment about whether the extrapolation should be linear or nonlinear. In some cases, consideration of several alternative approaches may be appropriate (EPA 2005). In the future, it may be possible to begin incorporating statistical approaches (e.g., Bayesi-

an methods, meta-analysis) to combine dose-response data from several studies when multiple studies are available and their integration into such procedures is feasible (NRC 2014).

Noncancer Effects

Point of Departure

The point of departure is the dose or exposure concentration associated with a critical effect used quantitatively as the basis for deriving a SMAC or SWEG. Ideally, the point of departure is obtained from human exposure data but may also be obtained from a well-conducted animal study in the species most representative of humans. Oftentimes, the key study and the overall data set are lacking in some critical aspect and, therefore, development of the exposure guideline will necessitate adjustment with uncertainty factors. Time scaling may be required when the data are for exposure durations different than those of interest. (See sections below on Exposure Duration Adjustments and Uncertainty Factors.)

Frequently, the point of departure will not be precisely defined in the available study reports. Depending on the SMAC or SWEG duration, this will necessitate estimation of a threshold for the effect or, for longer-term guidelines, a no-effect level. Threshold estimation usually entails selection of the highest dose or concentration that does not cause a relevant adverse effect for the longer-term SMACs or SWEGs. For an actual effect level, the point of departure for a short-term SMAC or SWEG generally will be the lowest reliable dose or concentration without serious or irreversible adverse health effects. Temporary discomfort may result but should not affect performance. Organoleptic considerations may impact the point of departure (see discussion later in this chapter on Organoleptic Effects).

The RD_{50} (concentration of a substance that reduces the respiratory rate of test organisms by 50%) has been used in setting occupational exposure levels for a number of irritants and may be appropriate as a point of departure for SMACs. Strong correlation has been shown between RD_{50} values in mice and acute inhalation lowest-observed-adverse-effect level (LOAEL) values in humans (Kuwabara et al. 2007). Currently, a calculation of $0.03 \times RD_{50}$ is suggested for setting occupational exposure limits, as originally proposed by Alarie (1981). However, this approach does not account for potential tissue damage from repeated exposure (Brüning et al. 2014) and would not be appropriate for longer-term SMACs.

For toxic effects other than cancer, the practice of risk assessment has been to estimate an acceptable exposure by dividing a no-observed-adverse-effect level (NOAEL) obtained from human studies or animal experiments by a set of uncertainty factors. A NOAEL is the highest experimental dose for which no difference in the occurrence of an adverse effect is observed relative to a control group. The NOAEL-based approach has come to be associated with the presumed existence of threshold doses—doses below which specific toxic effects

will not occur, even if exposure continues over a lifetime. The concept of a threshold is supported by the observation that many organisms have detoxification mechanisms or repair capacities to compensate for some degree of damage and still maintain normal function (Eaton and Gilbert 2013). In some cases, only a LOAEL will be available for risk assessment. A LOAEL generally corresponds to a response in the range of 1-10% of the maximal response and will require an uncertainty factor adjustment for extrapolation to a NOAEL. A free-standing LOAEL (from a single-dose study) should not be used as a point of departure unless it is supported by other data.

When sufficient dose-response data are available on a chemical, BMD or BMC methods should be used to derive an estimate of the exposure expected to cause a specified response incidence. Choice of the benchmark response level for the point of departure requires scientific judgments about the statistical and biological characteristics of the data set. An extra risk of 10% has commonly been used for quantal data, although biological considerations may indicate that 1% or 5% is more appropriate for the point of departure. For continuous data, the response corresponding to one standard deviation from the control mean has been recommended. Current EPA Benchmark Dose Guidance (EPA 2012a) should be consulted when using the benchmark dose approach for modeling quantal and continuous data sets. As needed, uncertainty factors are applied to obtain the final spacecraft exposure guideline.

Typically the BMD or BMC central estimate or the BMDL or BMCL (95% lower confidence limit of the BMD or BMC) for a specific biological effect is used as the point of departure. The central estimate is derived from the model fit, while the confidence limits are a computed statistical estimate. The BMDL (or BMCL) is often recommended because it has been shown to approximate the NOAEL (EPA 2002) and ensures with high confidence that the benchmark response is not exceeded (EPA 2012a). However, the size of the confidence interval is dependent on experimental design and procedures that provide a more precise central estimate also result in tighter confidence intervals. Thus, a study with few experimental doses and low numbers of animals may give broad confidence intervals around the central estimate resulting in an unrealistically low BMDL (or BMCL) as the point of departure. Careful consideration, including visual inspection of the resulting model fit, should be given to choosing the BMDL (or BMCL). In some cases the BMD (or BMC) may be a more reasonable choice for the point of departure.

The point of departure can also be derived from physiologically based pharmacokinetic (PBPK) models. Validated PBPK models can assess variability regarding uptake of chemicals, doses to target tissues, and time course for absorption, distribution, and excretion of a chemical of concern and its metabolites. Such mathematical models can be designed to estimate appropriate dose metrics, such as estimates of human equivalent doses from animal data, to address route-to-route extrapolations, and to facilitate high-to-low dose extrapolations. If a validated, peer-reviewed model is available, information from the model may be used in the

development of SMACs and SWEGs. Use of such models developed by NASA, but not formally peer reviewed, can be evaluated on a case-by-case basis.

In the absence of sufficient data, or when special circumstances dictate, the recommended default procedure for determining SMACs and SWEGs is essentially the NOAEL-based procedure recommended in previous guidance (NRC 1992; James and Gardner 1996).

Organoleptic Properties

Perceptions of an odor in spacecraft air or a taste in the drinking water are important chemical-specific factors that can affect both astronaut performance and quality of life. Although exposure to an unpleasant odor or taste may be acceptable for a short-term SMAC or SWEG, consideration of these chemical properties should be included in setting the longer-term guidelines. Astronauts are susceptible to dehydration in space and are encouraged to drink at least 2.8 L of water per day (which includes water for reconstituting food). Thus, NASA has used taste aversion and decreased water consumption in animal studies as the basis for establishing SWEGs (NRC 2000). Taste considerations are also addressed by the use of spaceflight-specific uncertainty factors (see section below on Spaceflight Factors).

No SMACs have been based on adverse effects occurring from odor. Adverse effects from odor are difficult to assess. Odor perception depends on the frequency, intensity, duration, and offensiveness of the odor and the sensitivity of the individual. Air concentration of a chemical above its odor threshold but well below the irritation threshold may elicit reports of perceived irritation that signify odor intolerance or annoyance (Dalton 2003). There is also evidence that cognitive factors, psychosocial factors, and personality variables can play a role in sensory perception (Dalton 1996, 2003). In addition, olfactory function in microgravity might be altered by congestion-related reductions in the airflow of the nasal passages. Chronic exposure to the same odor can decrease sensitivity because the olfactory system can rapidly adapt to a continuous odor. Such adaptation coupled with microgravity-related physiologic changes that alter the sense of smell could have implications for odor perception as a warning signal of a substance's presence (Brüning et al. 2014).

NASA's approach to dealing with air contaminants that have a significant odor at concentrations below those associated with adverse health effects has been to set SMACs on the basis of potential physical harm but to note the concentrations at which the presence of the chemical might create an unpleasant odor. The committee finds that this continues to be the most appropriate approach for NASA to use in addressing chemicals with odor issues for shorter-term exposure. For longer-term exposures, consideration of odor as an adverse effect might be appropriate, if it affects the well-being of the astronauts either directly (e.g., headache, nausea) or indirectly (e.g., reduced food or water consumption).

EXPOSURE CONSIDERATIONS

Inhalation, ingestion, and dermal routes are the three main pathways of exposure to airborne and waterborne contaminants for spacecraft occupants. Water contaminants enter the body mainly via ingestion, but their absorption and uptake are chemically dependent. The dermal route of exposure plays a minor role in the uptake of airborne and waterborne contaminants in spacecraft and, therefore, except in the case of spills, is less important in setting exposure guidelines. The main portal of entry for air pollutants is via the respiratory tract. Respiratory symptoms, allergic sensitization, or decrements in lung function can provide evidence of the impact of pollutants. Although spirometric measurements of lung function are the most widely used methods to assess particle- or gas-induced changes in the respiratory tract, numerous other non- or minimally invasive measurements have been developed to monitor adverse respiratory effects, including exhaled nitric oxide (index of inflammation), exhaled breath condensate, sputum induction, and nasal lavage (Mirowsky and Gordon 2015). Similar novel techniques have been developed and used for cardiology end points (Prisk and Migeotte 2013).

Under normal gravity, aerosols deposit in the human respiratory tract primarily by the processes of sedimentation, impaction, interception, and diffusion. However, under microgravity conditions, the amount and regional deposition of inhaled particles in the respiratory tract can be altered (Darquenne 2014). Sedimentation is gravity dependent, whereas impaction is due to the inability of individual particles to follow the curvature of air streamlines because of inertia, and the particles may hit and stick on the walls of airways. Diffusion is due to random (Brownian) motion of small particles (generally <0.2 μm) and is also independent of gravity. Thus, in a microgravity environment, sedimentation will not be a mechanism of particle deposition in the lung, and, thus, particle deposition will occur mainly due to inertial impaction and diffusion. The deposition of very small particles in the respiratory tract should not be significantly affected by microgravity conditions. Similarly, the interaction of inhaled gases within the respiratory tract is driven by diffusion and the chemical reactivity of the particular gas with the lining of the airways (e.g., mucous, surfactant, and epithelial cells) and, thus, will not be affected by microgravity. The absence of gravity can make a significant difference in regional particle deposition but the changes vary by particle size. Diffusion will account for most deposition for particles smaller than 0.5 μm, and research has shown that the microgravity environment has the largest effect in the lung periphery for particles in the size range of 0.5 to 3 μm (Darquenne 2014). Although the total deposition of 5-μm particles is decreased, the ratio of conducting-airway to alveolar-particle deposition increases because of a decrease in deposition via sedimentation in the low flow alveolar region. Thus, microgravity conditions will have minimal effect on particles in the smallest size range, whereas overall regional particle deposition is altered and total particle deposition is lower under microgravity conditions than at normal gravity (Darquenne 2014).

Importantly, because of the lack of particle deposition by sedimentation, the airborne concentration of particles from 5 to 100 µm in size and greater inside a spacecraft will be much higher under conditions of microgravity. These large particles can be irritating to the eyes and the respiratory tract. Transmission of infections could also increase because large droplets of contaminated saliva and respiratory secretions will also remain suspended in the atmosphere for a longer time under microgravity conditions than under normal conditions. Thus, changes in total and regional particle deposition, and the concentration of large particles in air, will influence the potential for adverse respiratory effects of airborne particles in the space environment.

Exposure Adjustments

Because studies will not be available on all of the exposure durations and routes of interest to NASA, it will be necessary for the agency to rely on the available data by making adjustments to account for the differences in exposure duration, exposure route, and species differences. Physiologically based pharmacokinetic models or dosimetry models can be used if adequate data are available (WHO 2010). In the absence of such models, mathematical adjustments can be used.

Exposure Duration Adjustments

As noted in previous guidance (NRC 1992), exposure duration adjustments depend on understanding the relationship between the concentration of the chemical and the duration of exposure leading to the adverse effect. For acute exposure adjustments, some health effects, such as irritation, are determined more by the concentration of the chemical than the duration of exposure at lower effect levels and are not expected to accumulate or to increase in severity over time, so a duration adjustment is unnecessary. For cumulative effects, the relationship between the exposure concentration and the duration is extrapolated using the equation $C^n \times t = k$, where C is the concentration of the chemical, t is the duration of exposure, k is a constant, and n is a chemical-specific (and even end-point-specific) exponent (ten Berge et al. 1986). The value of n should be derived empirically (e.g., probit analysis) from experiments that provide data on various concentrations and various durations of exposure. If data are inadequate to determine a value for n, default values of $n = 1$ for extrapolating from shorter to longer durations and $n = 3$ for extrapolating from longer to shorter durations have typically been used in setting acute exposure guidelines (e.g., NRC 2001; EPA 2014). This time-scaling approach is intended for extrapolations of relatively short durations (a few hours); data and scientific judgment are required to support this approach for scaling over longer time intervals.

For longer durations, adjustments are often needed to account for discontinuous exposure regimens used in experimental studies. In these cases, the point of departure is adjusted for a continuous exposure by taking into account the

exposure duration and the exposure frequency. The following equation may be used: $POD_{adj} = POD \times \frac{D}{24\ h} \times \frac{F}{7\ d}$; where POD_{adj} is the adjusted point of departure for a continuous exposure, POD is the point of departure based on a discontinuous exposure regimen, D is the exposure durations (hours/day), and F is the exposure frequency (days/week). Similar types of calculations for adjustment of 5 out of 7 days of dosing to 7 out of 7 days of exposure are made for oral exposure studies, as well as adjustments to calculate a human equivalent dose on the basis of water consumption (2.8 L/day) and body weight (70 kg).

Exposure Route Adjustments

In optimal cases, a point of departure for SWEGs will be derived from oral exposure studies in animals or from human data, whereas the point of departure for SMACs will be derived from inhalation exposure data. When data are lacking, however, some SWEGs and SMACs might be based on data from nonoral and noninhalation routes, respectively. For example, exposures of humans during spaceflight to contaminated water can happen by a variety of routes: inhalation, water consumption, and potentially dermal absorption. Where possible, conversions should be made to account for differences between routes of exposure for astronauts and those used in the animal studies from which a point of departure is derived. Assuming that the species-to-species conversion is made separately, it would be necessary to calculate a route-to-route conversion within species. Importantly, differences in rates of absorption for various routes (e.g., inhalation versus gastrointestinal) should be considered where possible.

Interspecies Adjustments

If adequate data on a chemical's toxicokinetics and toxicodynamics are available, a PBPK model or chemical-specific adjustments can be used to calculate a human equivalent dose or concentration from animal data (e.g, see EPA 1994, 2002, 2011; WHO 2010). In the absence of such data, interspecies conversions for exposures are often made on the basis of body weight or surface area differences between species (Allen et al. 1988; Travis and White 1988). EPA has recommended that a default approach for oral exposures is to use body weight scaling to the ¾ power ($BW^{3/4}$) (EPA 2011). This type of calculation is intended to correct for metabolic rate on the basis of body size. Because the estimates are related to basal metabolism and not xenobiotic metabolism, an assumption of concentration equivalence between species is made and remaining uncertainties are addressed by the use of an uncertainty factor (usually a factor lower than 10).

For inhalation exposures, algorithms have been used to estimate animal-to-human adjustments on the basis of anatomic and physiologic differences in the respiratory systems of experimental animals and humans, which are used in conjunction with a categorization scheme based on information on the chemical and physical properties of the chemical to determine appropriate dosimetry ad-

justments (e.g., see EPA 1994, 2002). An alternative to this categorization approach is a descriptor scheme based on the water solubility and reactivity of the gas (Medinsky and Bond 2001). Guidance on this scheme and advances in inhalation dosimetry are provided by EPA (2012b).

UNCERTAINTY FACTORS

Some degree of uncertainty is associated with the development of toxicity values for risk assessment. This uncertainty arises from the use of toxicity data from animal models to predict responses in humans, individual variability in the physiologic and toxicologic response, extrapolations regarding exposure duration-effect relationships, and difficulties identifying effect thresholds. These uncertainties have been addressed by the application of uncertainty factors that typically range over an order of magnitude (1 to 10) for each factor. A refinement to past practices is that data should be used whenever possible to select the magnitude of the uncertainty factor or to eliminate the need for it, including data on similar chemicals, toxicokinetic and toxicodynamic data, or other data that allow quantification of differences or variability. In the absence of data, default values are used. General guidance on the selection of uncertainty factors and the use of defaults for protecting occupational health (e.g., Dankovic et al. 2015) and public health (e.g., see WHO 2005, 2014; NRC 2009) is available. Guidance targeted at setting acute exposure guidelines for emergency planning also is available (see NRC 2001; Young et al. 2009). The use of uncertainty factors in these scenarios can be used as a guide for deriving SMACs and SWEGs, as discussed below for each of the defined sources of uncertainty. Both the nature of the toxicant and the duration of exposure are important considerations when deciding which uncertainty factors are relevant to deriving a particular exposure guideline.

Interspecies Differences

Inherent in the development of any toxicity guideline are the uncertainties related to variability in the toxic response among different species. Of special concern is the variability between laboratory animals and humans. An interspecies uncertainty factor is applied when data from laboratory animals are used as the basis for setting exposure guidelines for humans. Interspecies differences can be attributed in part to differences in dosimetry (dose to target) and dynamics (specific mechanism at the target). If sufficient toxicokinetic and toxicodynamic data are available, then a species-to-species conversion of the point of departure should be made on a quantitative basis. Calculation of human equivalent dose or concentration for use as the point of departure would account for the toxicokinetic differences such that only a factor for toxicodynamic differences would need to be applied. The World Health Organization (WHO 2005) has recommended factors of 4.0 for toxicokinetics and 2.5 for toxicodynamics for extrapolations from rats to humans on the basis of an approximate four-fold difference in parameters that determine clearance and elimination of chemicals

between these species. In many cases, insufficient information is available for making a quantitative estimate of the extrapolation from animals to humans. Thus, it is prudent to divide the point of departure by an uncertainty factor to account for unknown species differences because humans might be more sensitive than experimental animals.

In the absence of data, a default factor of 10 is commonly used to account for interspecies differences. Factors greater or less than 10 may also be used, depending on the nature of the toxicity. A factor of less than 10 may be applied if a human equivalent dose or concentration can be determined (e.g., from physiologically based pharmacokinetic models), data from the most sensitive species are used, if humans are shown to be less sensitive than animals, or if the mechanism of toxicity (e.g., direct-contact irritation) is not expected to differ between animal species and humans. With respect to the latter, a factor of 3 is appropriate for direct-contact irritants (Brüning et al. 2014) whereas for systemic effects a factor of 10 is appropriate. Metabolism and disposition of absorbed compounds may exhibit interspecies variability, indicating that humans are notably more, or less, susceptible than rodents.

Intraspecies Differences

An uncertainty factor commonly used in deriving exposure guidelines for the general public is a factor that accounts for the well-described variability among humans in sensitivity to specific substances. The factor is usually intended to account for people who may be more susceptible because of their age (e.g., newborns, infants, children, elderly), who may have preexisting health conditions, or who have other known factors that could increase their susceptibility to a particular chemical (e.g., certain genetic polymorphisms). Because of the relatively homogeneous and robust health status of the astronaut population, NASA has not routinely applied an uncertainty factor for intraspecies variability. However, such a factor is applied by NASA when there is evidence of biological variability relevant to the astronaut populations, such as sex differences or genetic factors that could affect response to a particular chemical. Significant progress in collecting "omics" data, such as genetic polymorphisms, is being made and NASA should include consideration of such data (for example, polymorphisms in metabolizing and antioxidant genes that may make individuals more or less susceptible to certain chemicals) when determining whether an uncertainty factor should be applied. More refined assessments of intraspecies variability will result from emerging evidence from in vitro and in vivo studies on the genetic and epigenetic basis for biological variability, as well as developments in modeling approaches to characterize human variability in response (Zeise et al. 2013).

Effect Levels to No-Effect Levels

The point of departure used in deriving SMACs and SWEGs may be based on a no-effect level (NOAEL or BMDL) or a lowest-observed-adverse-effect

level (LOAEL or BMD). The 7-day, 30-day, 180-day, and 1,000-day SMACs and the 10-day, 100-day, and 1,000-day SWEGs are exposure concentrations at which no adverse health effect is expected. The 1-day guideline, by definition, allows temporary discomfort as long as no effects occur on crew judgement, performance, or ability to respond to an emergency. As such, the 1-day guideline may be derived from an effect level provided that the effect is within the definition or of lesser severity. This may involve a discussion about the exposure-response relationship (steepness of the exposure-response curve), if such data are available. However, for specific exposure guidelines, an uncertainty factor may be appropriate if the effects at the point of departure are more severe than those defined for that SMAC or SWEG level.

If an effect level rather than a no-effect level is chosen as the point of departure, an uncertainty factor is used. An uncertainty factor of 10 is generally used to extrapolate from a LOAEL to a NOAEL. However, some investigators have suggested that a factor of 3 to 5 would be more appropriate because comparisons of LOAELs and NOAELs indicate that a LOAEL is rarely more than five- to six-fold of the NOAEL and is usually closer to a value of 3 (Abdel-Rahman and Kadry 1995; ECETOC 2003). Use of a no-effect level is often advantageous because it is based on experimental data, whereas effect levels require judgment calls about the degree to which they should be reduced to approximate a no-effect level. For SMACs and SWEGs, a factor of 3 or 10 should be used to reduce an effect level to an appropriate no-effect level. Such a factor would not be required if a BMD or BMC is used at the point of departure, and may not be needed for derivation of a 1-day SMAC or SWEG if the critical effect is consistent with the definition of the 1-day guidelines.

Exposure Duration Differences

Sometimes the database on a chemical will not include studies that have evaluated exposure durations relevant to the SMACs or SWEGs, so a study with the duration closest to the relevant SMAC or SWEG is used. If data are available, an adjustment to account for the difference in duration is the preferred approach (see earlier section on Exposure Duration Adjustments). In the absence of data, an uncertainty factor may be applied to account for duration extrapolation from experimental data to the relevant duration of the SMAC or SWEG. The magnitude of this factor will vary on a case-by-case basis depending on the available data for each guideline scenario. However, the uncertainty factor may not be required if data indicate that the nature of the effects would not differ substantially with prolonged exposure or that toxic metabolites or damage will not accumulate.

SPACEFLIGHT FACTORS

Spaceflight factors are uncertainty factors used by NASA to address effects of a chemical that are exacerbated by the physiological changes and stress-

es of spaceflight (NRC 1992). The physiologic changes and stresses that occur from spaceflight (including takeoff, microgravity, radiation, reentry, and return to normal gravity) have been well documented (e.g., see NRC 1992; IOM 2001; Buckey 2006; Baker et al. 2008; Williams et al. 2009). Some effects begin to occur immediately after launch and others develop more gradually with prolonged spaceflight. Two significant immediate effects are cardiovascular fluid shift and neurovestibular disturbances. The fluid shift is due to the loss of hydrostatic gradients, which causes about 2 L of bodily fluids to move from the lower part of the body into the upper part, resulting in a sensation of fullness in the head and nasal congestion. The discomfort associated with the shift is reported to be short term, and becomes tolerable as new set points for fluid regulation are established (Baker et al. 2008). However, the fluid shift contributes to other physiologic effects from prolonged spaceflight, such as cardiovascular and hematologic changes (discussed below).

Another significant short-term effect on astronauts is space motion sickness. Its symptoms and severity vary, but generally include sensitivity to motion and head movements, headache, stomach awareness, diminished appetite, nausea, and vomiting (NRC 1992; Baker et al. 2008). Symptoms generally last 2 to 3 days, but have been reported to persist for up to 10 days. The effects can lead to decreased food and water intake, resulting in a reduction in blood volume and decrease in overall crew member performance. A common treatment for this condition is intramuscular injections of promethazine (Baker et al. 2008).

Some of the major human physiologic changes resulting from long-term spaceflight are presented in Box 2-1. The six effects for which spaceflight factors have been used by NASA include loss of bone mineral density, renal effects, cardiovascular effects, alterations in red-blood-cell mass, effects on immune response, and dehydration due to decreased water consumption. A spaceflight factor is used when there is evidence that a chemical could exacerbate one of these conditions. For example, a spaceflight factor for cardiac effects would be applied if a chemical has been shown to cause cardiac sensitization in animals. (See Table 2-1 for examples of chemicals for which spaceflight factors were applied in calculating SMACs or SWEGs.) With the exception of cardiac effects, a default value of 3 is typically used for these spaceflight factors for the reasons described in the sections below. When relevant data on the effects of microgravity on bodily functions are available, it may be possible to quantify the potential effects rather than rely on default adjustments in setting short-duration guidelines.

Consideration of all these physiologic and behavioral changes is complex and particularly difficult when considering SMACs and SWEGs for 1,000 days. Few data are available on the effects from prolonged exposure to microgravity such that any guidelines derived are likely to be associated with a high degree of uncertainty.

Loss of Bone Mineral Density

Studies of humans and animals have demonstrated significant and contin-

uous loss of bone mineral density from prolonged exposure to microgravity (NRC 1992). Bone demineralization begins immediately, and primarily affects the weight-bearing bones of the lower extremities, pelvis, and lumbar spine. Average bone losses are about 1-2% per month. For a typical mission of about 6 months, losses range from 8% to 12% depending on the bone region (see reviews by Shackelford 2008; Williams et al. 2009). A large degree of variability in demineralization between individuals and among bone regions within the same individual has been observed, suggesting phenotypic variations in susceptibility to microgravity-induced bone mineral density loss (IOM 2001; Shackelford 2008). However, no substantial differences have been found between male and female astronauts (Smith et al. 2014). Loss of bone mass is well known from reduced stress on the musculoskeletal system (e.g., bed rest, professional scuba diving); however, the mechanisms underlying microgravity-induced bone mineral loss are not fully understood (Baker et al. 2008). Advancements in analysis of metabolic markers have provided greater understanding of the process, which involves both resorption of bone as well as reduction in intestinal absorption of calcium (likely as a result of higher blood calcium level) (Baker et al. 2008). The process has a long-term effect on overall bone density, because bone mineralization occurs more slowly than demineralization. In general, it takes 6 months to 3 years for the majority of astronauts to return to baseline levels, and some have never fully recovered (Shackelford 2008).

Renal Effects

Physiologic and behavioral changes in microgravity directly affect renal function as well as increase the risk of renal stone formation (Baker et al. 2008; Jones et al. 2008; Liakopoulos et al. 2012). Thoracic fluid shift and space motion sickness reduce thirst and fluid intake. In addition, increased vascular permeability and transfer of fluid to intracellular and interstitial compartments decrease plasma volume by about 12% of normal. Antidiuretic hormone is typically elevated during spaceflight and is also increased by nausea from space motion sickness. Diuretic (urinary excretion of water) and natriuretic (urinary excretion of sodium) responses and urine volume are reduced in microgravity. Glomerular filtration rate increases during the first 2 days in microgravity, but is only slightly elevated after a longer duration. Daily sodium balance in microgravity is positive for greater sodium reabsorption in the kidney and lower excretion in the urine, and the retained sodium is transferred to extravascular spaces. Hypercalciuria from loss of bone mass may result in reduced water reabsorption by the kidney. The reduced plasma volume results in elevated antidiuretic hormone release and activation of the renin-angiotensin-aldosterone system. Astronauts have thus been described as having renal responses similar to those with heart failure (edema, sodium retention, low blood volume, and sympathetic nervous system activation) without having a disease (Liakopoulos et al. 2012).

BOX 2-1 Some Major Human Physiologic and Behavioral Changes Resulting from Extended Travel in Earth Orbit

Musculoskeletal System
- Loss of bone mineral density
- Loss of skeletal muscle

Cardiovascular System
- Orthostatic hypotension
- Loss of hydrostatic pressure

Pulmonary System
- Changes in pulmonary circulation and gas exchange

Alimentary System
- Ileus
- Decrease in absorption or malabsorption

Nervous System
- Ataxia
- Motion sickness
- Disturbed fine motor and gross motor functions
- Altered sleep-circadian rhythm and sleep deprivation

Reproductive System
- Effects of radiation on gametes

Urinary System
- Renal calculi

Hematologic and Immunologic Systems
- Anemia
- Potential immunologic depression

Behavioral Health (IOM 2014)
- Adverse behavioral conditions and psychiatric disorders
- Performance errors due to fatigue
- Performance errors due to inadequate cooperation, communication, and psychosocial adaptation

SOURCE: Adapted from IOM (2001).

TABLE 2-1 Chemicals for which Spaceflight Factors Were Used to Derive SMACs or SWEGs

Spaceflight Factor	Chemicals
Loss of bone mineral density	Cadmium
Renal effects	Barium, chloroform, dichloroacetylene, methylene chloride, octamethyltrisiloxane, tert-butanol, trichloroethylene, ethylene glycol, and mercury
Cardiovascular effects	Barium, freon 11, freon 12, freon 21, and freon 113
Blood cells or volume	Benzene, bromotrifluoromethane, di-n-butyl phthalate, unsymmetrical dimethylhydrazine, 2-ethoxyethanol, isoprene, indole, nitromethane, and trichloroethylene
Immune response	Nickel, 2-mercaptobenzothiazole
Organoleptic effects	C1-C4 mono-, di-, and tri-alkylamines, ammonia, antimony, barium, cadmium, dichloromethane, and silver

A secondary effect of bone demineralization is hypercalciuria, which increases the risk of renal stone formation. In particular, mobilization of calcium and phosphate from bones increases stone-forming salts, such as calcium oxalate and calcium phosphate, in the urine. Higher urinary specific gravity increases concentrations of these salts as well as others associated with stone formation (uric acid, sodium urate, and struvite). Low urinary pH and citrate concentrations resulting from microgravity also promote stone formation. Finally, nanobacteria appear to promote stone formation by enhancing the concentration and precipitation of calcium phosphate (Ciftcioglu et al. 2005; Liakopoulos et al. 2012). These very small agents resemble microbes with relatively slow replication rates, although multiplication is enhanced in microgravity (Ciftcioglu et al. 2005).

Jones et al. (2008) studied the effects of spaceflight on renal stone formation by measuring urinary biomarkers of renal effects taken from 322 astronauts before and after short-duration flights on the Space Shuttle and comparing them with benchmark risk thresholds for the biomarkers. Measures of hypercalciuria indicated a preflight risk of renal stone formation of 20.8% compared with a postflight risk of 38.9%. Supersaturation values for calcium oxalate indicated a preflight risk of 25.6% and a postflight risk of 46.2%; for uric acid, preflight risk was 32.6% and postflight risk was 48.6%. Astronaut candidates are screened for susceptibility to renal stone formation (e.g., anatomical factors, underlying renal disease, metabolic disorders) and those found to be at increased risk are excluded from acceptance. As a result, the baseline rate of stone formation is lower in the astronaut population than in the general population (Jones et al. 2008; NRC 2008a). Due to the increased risk of renal stone formation, NASA has recommended that astronauts consume at least 2.8 L of water per day to mitigate the risk (NRC 2000).

In addition to renal stone formations, some evidence from studies of animals indicates possible renal damage in microgravity. Simulated microgravity by tail suspension of male rats for 8 weeks resulted in histopathologic changes, such as glomerular atrophy; renal tubular epithelial cell extension, degeneration, and necrosis; and interstitial edema and hemorrhage (Ding et al. 2011). An increase in apoptosis in renal tissue was indicated by a 3.2-fold increase in protein caspase-3 in renal tissue of the tail-suspended group, which is an indication of renal impairment and damage. The study found that resistance training with tail suspension reduced the amount of histopathologic damage observed.

Such severe effects on the kidneys have not been reported in humans after spaceflight, although possible effects on the kidneys were suggested by proteomic analysis of the urine of 10 cosmonauts after 169-199 days at the International Space Station (Pastushkova et al. 2013). This study detected three urinary proteins that were absent prior to spaceflight. Two were present 1 day after return but not after 7 days and were indicative of oxidative stress (afamin) and hypercalcemia (aquaporin-2). A third protein (aminopeptidase A) appeared after 7 days and was thought to reflect possible tubular dysfunction or hypoxia of

renal cells. An earlier study of two cosmonauts on the Mir space station reported increased urinary albumin excretion; however, subsequent studies on those visiting the Mir space station have reported a decrease in albumin excretion (Liakopoulos et al. 2012).

Thus, a spaceflight factor for substances that affect the kidneys is justified because of the stresses produced on this organ in spaceflight. In addition, substances that might decrease fluid intake (including taste or odor), increase urinary solute concentrations, or decrease urinary pH should also be considered for their effects on the kidneys and the risk of renal stone formation.

Cardiovascular Effects

As noted earlier, weightlessness causes fluid shifts toward the upper part of the body and from extravascular to intravascular spaces. These alterations lead to changes in stroke volume and cardiac output. NASA is concerned about potentially serious cardiac effects, such as impaired cardiovascular responses to orthostatic stress, diminished cardiac function, manifestation of previously asymptomatic cardiovascular disease, dysrhythmias, and impaired cardiovascular responses to exercise (Levine et al. 1996). Norsk et al. (2015) evaluated measurements of stroke volume and cardiac output taken from eight male astronauts before launch, once between 85 and 192 days at the International Space Station, and 2 months after landing. Cardiac stroke volume increased by 35% and cardiac output increased by 41% while on the space station, which is more than has been measured for shorter durations in space. A 39% reduction in systemic vascular resistance was found, but heart rate and catecholamine concentrations were similar to preflight measures. In addition, electrocardiographic monitoring during spaceflight has detected premature atrial contractions, premature ventricular contractions, and ST-segment or T-wave changes; the changes generally occurred during strenuous or stressful activity (Hamilton 2008).

Mandsager et al. (2015) reviewed nine studies that measured arterial blood pressure and heart rate during spaceflight. The measures taken from spaceflights of less than 1 month in duration were variable and inconsistent; blood-pressure and heart-rate measurements were increased or unchanged. Studies of longer-duration flights had more consistent results, but were fewer in number (n = 3). These studies reported that heart rate was unchanged and that blood pressure was unchanged or reduced.

Astronaut candidates are screened for overt cardiovascular disease and spaceflight crew members undergo annual medical evaluations to certify their cardiovascular fitness, but the screening tests may not be sufficient for ruling out the possibility of cardiovascular events on orbit (Hamilton 2008). Because the nature of the cardiovascular alterations can lead to serious effects on health, a spaceflight factor of 5 rather than 3 has been used by NASA.

Alterations in Red-Blood-Cell Mass

Astronauts lose about 10% of their red-blood-cell mass in the first week of spaceflight (Baker et al. 2008). The mechanism appears to involve plasma extravasation from the vascular space to the intracellular space, resulting in increased hematocrit and inhibition of erythropoietin. The reduction in red-blood-cell mass appears to result from selective hemolytic destruction of the youngest erythrocytes and sequestration of red blood cells in the spleen.

Effects on Immune Response

The immune system protects against pathogens, supports tissue repair and wound healing after trauma, performs surveillance and removal of incipient cancer cells, and maintains a balanced microbiome (e.g., gastrointestinal, lung, oral, genital) that is essential for normal physiological activity. Disordered immunity can result in increased susceptibility to pathogens, increased risk of cancer, increased risk of autoimmune disease, increased allergic reactions, and systemic inflammation leading to various diseases. Importantly, because proinflammatory cytokines can alter xenobiotic metabolism, inflammation can modify the disposition of xenobiotics within the body.

Recent discoveries in immunology are factors to consider when assessing chemicals that could affect the immune system, for example, the roles of T-regulatory cells, B-regulatory (B10) cells, TH17 cells in innate immunity, macrophages and their polarization states, dendritic cell subsets, innate lymphoid cells, and the microbiome as determinants of immunity. Also, the roles of genetics, epigenetics, nutritional status, oxidative stress, aging, and gender are known to modify immune response. Many more recently discovered cytokines and immune system modulators have been shown to be important in both acute and chronic immune disorders.

Astronauts travel and live in enclosed ecosystems of limited volume, and a number of environmental and physical factors could affect their immunologic competence or transmission of infectious agents. For example, astronauts routinely experience nasal and ocular irritation which could increase the potential for infection via the mucosal membranes; exposure to large particulates (>100 μm in diameter) is greater because of the microgravity environment; dermal abrasions and irritation are common; the humidity of the enclosed system can support the growth of microbial ecosystems; options for personal hygiene are restricted; and the close quarters means there is limited physical separation between galley and toilet facilities and among astronauts. Astronauts also experience chronic stress and isolation, factors known to cause immune alterations.

Rodent studies using spaceflight and microgravity models have reported impaired immune responses. For example, splenocyte immunophenotypes and cytokine levels of spaceflight mice differ from ground controls (Hwang et al. 2015). Studies in astronauts in space environments for both short and extended

periods have found alterations in circulating leukocyte subpopulations and certain cytokine concentrations (e.g., TNFα, IL-8, IL-1ra, Tpo) that can be significant (Crucian et al. 2013, 2014), suggesting disordered immune responses. Moreover, lymphocytes are known to be highly sensitive to ionizing radiation, and dysregulation of T lymphocytes during spaceflight is also well documented. Reactivation of latent viruses (e.g., Epstein-Barr virus, cytomegalovirus, herpes viruses) is a common occurrence among astronauts with extended stays in space, and this has been most closely associated with stress biomarkers. Stress hormones are released on a sustained basis during spaceflight (Sams and Pierson 2008; Crucian et al. 2013, 2014).

On two occasions, NASA has applied a "hypersensitivity factor" in setting SWEGs for chemicals known to cause allergic contract dermatitis—nickel and 2-mercaptobenzothiazole (NRC 2004). Few data were available to determine whether ingestion of water contaminated with these chemicals could induce an allergic response. Although the critical end point chosen as the basis of the SWEGs was *not* an allergic reaction, a factor of 3 was applied in both cases to at least partially protect astronauts from such a response. The committee finds this appropriate for immune responses involving allergic reactions.

Odor and Taste Considerations

Several contaminants found on spacecraft have disagreeable odors or are unpalatable. In many cases, the odor or taste threshold for the chemical is at a concentration lower than that associated with adverse health effects. However, the organoleptic properties of the chemical could have effects on behavior that might lead to adverse effects. For example, astronauts might consume less than the recommended 2.8 L of water per day if the water is unpalatable, which could lead to dehydration.

NASA differs in its approach to evaluating the organoleptic effects of air and water contaminants. "Crews will be forced to breathe air with an unpleasant smell when their supply of fresh air or their respirators are expended, even though the air is not harmful. They will adapt to the presence of a continuous odor. However, they can choose not to ingest water that tastes or smells unpleasant, even if it is not harmful. They will not adapt to this because they experience the odor only when trying to drink water" (NRC 2008b, pp. 79-80). Thus, NASA uses evidence of reduced water consumption as a basis for setting SWEGs and also applies a spaceflight factor to reduce the potential for astronaut dehydration.

Hepatic Effects

The liver is a critical multifunctional organ for processing and metabolism of nutrients, drugs, and xenobiotics; synthesis and regulation of lipoproteins; regulation of blood sugar; reuse and elimination of waste materials, such as de-

graded red blood cells; and making bile for emulsifying fats in digestion. The liver is particularly vulnerable to toxicant exposure because of the first pass effect of blood flow from the gastrointestinal tract and because of its high metabolic activity for xenobiotics, potentially resulting in greater exposure of the liver to toxic metabolites and intermediates for some substances. To date, NASA has not applied a spaceflight factor for hepatic effects in setting any SMACs or SWEGs, but it should be a consideration in the future. Spaceflight adds additional stresses on the body and the liver both directly and indirectly. In particular, fluid shifts in the body and space motion sickness may result in reduced food intake and nutritional status and reduced fluid consumption. In addition, loss of bone mass and muscle atrophy affect calcium and amino acid regulation, and astronauts reportedly land in a protein-depleted state (Stein and Schluter 2006).

These stresses in general may affect the normal function of the liver as well as potentially increase its susceptibility to chemical injury, depending on a specific chemical's mode of toxic action. Studies examining spaceflight effects on the liver have been conducted largely in laboratory animals, primarily male rats (Merrill et al. 1990; Hollander et al. 1998; Brunner et al. 2000; Rabot et al. 2000; Baba et al. 2008; Gridley et al. 2008; Baqai et al. 2009; Jain et al. 2011; Wei et al. 2012; Bederman et al. 2013). Despite body mass reductions reported in some studies (probably related to decreased food intake), most studies do not report reduction in liver mass. Studies in rats have also reported reductions in cytochrome P450, as well as antioxidants (glutathione and glutathione-S-transferase, superoxide dismutase, and catalase) after spaceflight (Hollander et al. 1998; Rabot et al. 2000). Baba et al. (2008) reported an increase in gene expression for CYP4A1 (rat-specific P450) and other stress-related proteins in rats after a 9-day spaceflight. Other studies in rats involving simulated hind limb weightlessness by tail suspension report reductions in phase I oxidative metabolism (Wei et al. 2012) but not phase II metabolism involving conjugation reactions (Brunner et al. 2000).

Spaceflight and weightlessness also result in increased liver and muscle glycogen in rats, which show a shift toward glycolysis and a decrease in lipid oxidation as a fuel source in muscles. According to Stein and Wade (2005), an oversupply of glucose leads to insulin resistance and fat accumulation in muscles (similar to a diabetic state), consistent with observations in Space Shuttle astronauts and cosmonauts on long-term missions at the Mir space station. Stein and Wade (2005) attributed increased glucose concentrations in rats to excess amino acids as a result of reduced requirements for protein turnover and metabolism by the muscles. Astronauts then enter an anabolic phase in the postflight period in which amino acids are limited, resulting in depressed concentrations of plasma proteins even at 6 days postflight as the body attempts to recover by rebuilding muscle mass (Stein and Schluter 2006). Radiation is another possible stressor during spaceflight that might contribute to effects on liver metabolism (Gridley et al. 2008).

Limitations in assessing whether a spaceflight factor is justified for substances that affect the liver include the small numbers of animals used in the studies and fewer data on species other than male Sprague Dawley rats; questions about whether the observed effects, which were measured after spaceflight, might be attributed to readaptation to gravity rather than from microgravity (Hollander et al. 1998; Macho et al. 2001); and lack of information on the diet and food consumption, which are factors than can also affect liver function. Effects of spaceflight observed in animal studies that might be attributed to stress during re-entry (e.g., reduced anti-oxidant defense capacity [Hollander et al. 1998]) may still constitute increased vulnerability of the liver, although this period may be of less concern because of its short duration at the end of the mission, after which astronauts would be under NASA medical care for the readaptation period.

Whether an additional uncertainty factor should be considered in deriving spacecraft exposure guidelines for substances that affect the liver will depend on the specific mode of action of the chemical at low concentrations. In particular, substances that might exacerbate the effects of spaceflight on the liver potentially include those that produce oxidative stress or require phase I enzymes for detoxification, or those that might increase insulin resistance or affect insulin or blood sugar levels. Substances that have a mode of action related to formation of more toxic intermediates by phase I oxidation, on the other hand, may be less toxic.

The liver may have specific susceptibility for mixtures of substances because of its high metabolic capacity and the first pass effect for ingested substances, particularly those that are metabolized (Jaescheke 2013). In addition, although the critical point of departure may be based on another end point than the liver, if the mode of action involves liver metabolism, alterations of liver function during spaceflight could have an effect. Therefore, the mode of action of chemicals that might involve the liver should be considered in assessing individual chemicals as well as when considering mixtures of chemicals.

MIXTURES

SMACs and SWEGs are established for single chemicals even though they occur in mixtures with other components in spacecraft water and air. Interactions with other components include chemicals within and across media, with pharmaceuticals, with physical stressors (e.g., noise, radiation), and with microbes. Previous guidance has recommended analysis of chemical mixtures by use of dose addition for chemicals that have similar modes of action or act on the same target organ (NRC 2000). Substances can be grouped together to assess their respective concentrations, C_i, using the following formula:

$$\frac{C_1}{SWEG_1} + \frac{C_2}{SWEG_2} + \frac{C_k}{SWEG_k} \leq 1$$

where C is the measured concentration of a particular chemical in water (or air), which is divided by the corresponding SWEG (or SMAC) for that chemical. A separate group limit could be established for each group with a particular mode of action to restrict the concentrations of the individual components of the mixture to those that are more likely to have additive effects even at their respective NOAELs. When the joint action of chemicals in a mixture does not align with the default additivity assumption, further evaluation is warranted. A different approach is used to assess potential risks from mixtures of chemicals that have dissimilar toxicity. In this approach, the probability of observing a toxic response for each chemical component in the mixture is estimated and then the component risks are summed to estimate total risk from exposure to the mixture (EPA 2000). Such methods would be appropriate for NASA to use when considering chemical mixtures that might be found aboard spacecraft.

FINDINGS AND RECOMMENDATIONS

The approach to deriving SMACs and SWEGs remains largely the same as in the past, but a number of refinements to the process have since been developed to help improve the basis of the exposure guidelines. The thrust of these refinements is directed toward giving preference to data-driven approaches, quantitative analysis over qualitative analysis, and better transparency in how the data are used to select critical end points and make judgments about extrapolations, assumptions, and uncertainties. Emphasis is now being placed on integrating information on mode of action to inform hazard identification and to make judgments about dose-response relationships and susceptibility. NASA should incorporate these advances to the extent possible in its assessment practices to ensure the scientific credibility of its SMACs and SWEGs. Appendix B provides example outlines for how future SMAC and SWEG documents might be organized.

Recommendations: Key refinements that should be incorporated in updating existing SMACs and SWEGs and in developing guidelines for new chemicals include the following:

- *NASA should provide better documentation of its strategy for conducting literature searches and the basis for selecting studies for inclusion in the chemical assessment. For the literature searches, a template should be created to describe the search approach to ensure that relevant information is captured. At a minimum, NASA should specify the databases and sources that were searched, describe the search strategies for each database and source searched, and specify the dates of each search and the publication dates included.*
- *NASA should ensure that key decisions made in deriving SMACs and SWEGs are explained and justified. Examples of key decision points are the se-*

lection of the point of departure, selection of uncertainty and spaceflight factors, and extrapolation procedures.

- *An additional spaceflight factor for susceptibility or exacerbation of effects on liver function should be added to the special spaceflight considerations used in deriving SMACs and SWEGs.*
- *The values for uncertainty and spaceflight factors should be selected on the basis of chemical-specific data to the extent possible. The factors should be considered in context with each other to avoid making duplicative adjustments for the same uncertainty.*

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3

Selecting and Prioritizing Contaminants for Assessment

Air and water contaminants are identified by the National Aeronautics and Space Administration (NASA) through a comprehensive assessment of potential sources of contaminants aboard spacecraft (NRC 1992, 2000; Kahn-Mayberry et al. 2011). The process is complex, requiring an understanding of all the materials and components onboard spacecraft, the environmental control and life-support system of space vehicles, processes that might occur in space, experiments to be performed, and a variety of other scenarios. Major contaminants are chemicals produced from off-gassing of cabin materials, components, and equipment; metabolic waste products from crew members; chemicals formed in the water treatment system; chemicals added to the water supply to retard bacterial growth; and compounds formed by chemical and physical processes in the cabin air. Scenarios considered are continuous or frequent releases from routine operations and activities; inadvertent, accidental, or emergency releases; and releases from experiments performed on the space station. Information about known and new sources of contaminants has been accumulated over decades of spaceflight experience and from environmental sampling and monitoring (Kahn-Mayberry et al. 2011).

Because NASA has insufficient resources to conduct comprehensive risk assessments of all potential air and water contaminants, it is important that priorities be established to focus on the chemicals that pose the greatest potential human health risk. The earlier guidance from the National Research Council (NRC) on setting spacecraft water exposure guidelines found that there are many approaches to setting priorities for choosing candidates for formal risk assessment (NRC 2000). The approaches range in complexity and each has its advantages and disadvantages. The three approaches to priority setting considered by the previous committee included an ad hoc approach, an ad hoc approach with factors specified, and a formal system with parameters, weights, and interrelationships specified. Key elements of each approach include the following:

- **Ad Hoc Approach:** Candidate chemicals are proposed as the chemicals become of interest to NASA. They might be identified through screening of

potential sources of atmospheric or water contaminants or from monitoring of the environmental control and life-support systems. Periodically a chemical is chosen from the list of candidates by NASA on the basis of informed judgment using subjective and qualitative information. The parameters or the data elements on which candidates are chosen are not specified and the candidates are not weighed against each other in a quantitative sense.

- **Ad Hoc Approach with Factors Specified:** A slightly more formal approach to setting priorities is for NASA to specify the parameters it considers in setting priorities. Such parameters might include evidence of exposure, magnitude of routine and accidental exposure, short- and long-term health effects, ability to monitor and control exposure, and the need to have the chemical on board a spacecraft.
- **Formal System:** Priorities are based on a specified set of parameters, a formula is used to combine scores for various parameters, and the relationship and weighting of the parameters are specified. The formula could be a simple sum of scores of various parameters or a more formal complex formula in which parameters are given unequal weights and their relationships are other than additive. Parameters that might be relevant for NASA's purposes include likelihood of routine exposure, medical intelligence from ground-based or flight-based experience, likelihood of unusual exposure, severity of toxicity, design requirements (e.g., the capacity for controlling and eliminating exposures), special spaceflight considerations, and spaceflight experience (NRC 2000).

Previous NRC guidance has encouraged flexibility in selecting chemicals as a means to increasing the effectiveness of risk assessment. The process should allow for new information on changes in parameters, changes in information on specific chemicals, and the addition of new chemicals for consideration. For example, a series of priority rankings based on changes in parameters considered, their weighting, or their relationships could be developed. Priority rankings could then be compared in a way akin to sensitivity analysis in mathematical risk assessment.

Similar conclusions about available schemes were drawn by other NRC committees formed to provide the US Environmental Protection Agency with assistance in establishing a priority-setting process for drinking water contaminants (NRC 1999, 2001). Those committees evaluated existing schemes and explored the development of alternative approaches and found that there are no sharp boundaries between the types of schemes, as all involve a mix of data and to some degree expert judgment. The main differences are the specific mix of parameters considered and the extent to which explicit or implicit judgments come together to produce reliable results. The committee concluded that the output of most prioritization schemes is so uncertain that they are only useful in making preliminary screening assessments or classifications and should not be used for sorting contaminants in a specific order.

FINDINGS AND RECOMMENDATIONS

The options for choosing candidate chemicals for risk assessment remain the same as previously available. One choice is subjective and is based on informed expert judgment. The second approach provides a slightly more formal approach, in which parameters for making the decision are specified but their weights and interrelationships are not. The third approach is more formulaic and involves specifying and quantifying the elements that are considered and using a weighting system for ranking contaminants.

Recommendation: The committee endorses NASA's use of a combination of these approaches to select chemicals for risk assessment. The process should be described to support the selection process.

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Appendix A

Biographical Information on the Committee on Spacecraft Exposure Guidelines

Edward C. Bishop is a risk management consultant for HDR, Inc. He has diverse experience in industrial hygiene, environmental compliance, emergency response, and risk assessment. He had a 20-year career in the US Air Force, in which he held a number of positions, including senior bioenvironmental engineering program manager in the Office of the Air Force Surgeon General. In that position, he developed and managed occupational health, industrial hygiene, and environmental protection programs worldwide. Dr. Bishop has served on several committees of the National Academies of Sciences, Engineering, and Medicine, including service as chair of the Committee on Acute Exposure Guideline Levels. He is currently a member of the Committee on Chemical Demilitarization. He received his MS in engineering from the University of California, Los Angeles, and his PhD in environmental health sciences from the University of California, Berkeley.

Terry Gordon is a professor in the Department of Environmental Medicine at the New York University School of Medicine. He uses both human and animal experimental models to study the genetic susceptibility underlying the adverse pulmonary and cardiac effects of environmental and occupational air pollutants, such as ozone, beryllium, and nanoparticles. Dr. Gordon is chair of the Threshold Limit Value – Chemical Substances Committee of the American Conference of Governmental Industrial Hygienists and is a former president of the Inhalation Specialty Section of the Society of Toxicology. He received his MS in toxicology from the University of Michigan and his PhD in toxicology from the Massachusetts Institute of Technology.

Bernard A. Harris, Jr., is chief executive officer and managing partner of Vesalius Ventures, a venture capital firm that supports and invests in early to mid-stage health care technologies and companies. He is a former astronaut, who has logged more than 438 hours in space, and conducted the first telemedicine conference from space with the Mayo Clinic. He also worked for NASA for 10 years, conducting research in musculoskeletal physiology and disuse osteoporo-

sis. He led the Exercise Countermeasure Project, which involved clinical investigations into physiological space adaptation and the development of in-flight medical devices to extend the duration of astronaut stays in space. Dr. Harris is a former vice president and chief scientist of SPACEHAB, Inc., a venture-backed innovative space commercialization company, and a former vice president of business development for Space Media, Inc., an informatics company. He received an MD from Texas Tech University School of Medicine, an MMS from the University of Texas Medical Branch-Galveston, and an MBA from the University of Houston, and trained in internal medicine at the Mayo Clinic.

Terrance J. Kavanagh is a professor in the Department of Environmental and Occupational Health Sciences and adjunct professor of pulmonary and critical care medicine at the University of Washington (UW). He currently serves as director of the UW Center for Ecogenetics and Environmental Health, and Director of the UW Nanotoxicology Center. He is board certified in toxicology, with expertise in animal models, analytical cytology, in vitro toxicology, and gene-environment interactions. His areas of research interest include glutathione metabolism, free radical biology, oxidative stress biomarkers, toxicogenomics, systems genetics, and nanotoxicology. Dr. Kavanagh is a former president of the Mechanisms Specialty Section of the Society of Toxicology and of the Pacific Northwest Association of Toxicologists. He received his MS in physiology and PhD in environmental toxicology and genetics from Michigan State University.

Margaret M. MacDonell is a program manager in the Environmental Science Division of Argonne National Laboratory. Professional interests include integrated health impact analyses and environmental sustainability; environmental fate, exposure, and cumulative risk evaluations for multiple stressors, including chemical mixtures, nanomaterials, and other hazards (including those related to energy development); and community involvement for environmental health protection. Dr. MacDonell has conducted health risk analyses at legacy waste sites for the US Department of Energy and Army Corps of Engineers; developed risk training workshops for practitioners and managers; and collaborated with Environmental Protection Agency (EPA) Centers on cumulative risk assessment and acute and short-term exposure advisories for chemical, radiological, and biological contaminants. She has served on several Academies committees, including the Committee on Acute Exposure Guideline Levels and the Committee to Review the IRIS Process, and currently serves on the Committee on Toxicology. Dr. MacDonell received her MS in environmental health engineering from Notre Dame and her PhD in environmental health engineering from Northwestern University.

Martin A. Philbert is dean of the University of Michigan School of Public Health, and is a professor of toxicology. His research interests include experimental neuropathology, nitro compound–induced encephalopathies, mitochondrial mechanisms in non-neuronal cell death, and nanostructure-based imaging

and treatment of tumors of malignant gliomas. He is currently involved in developing magnetically responsive optical nanoprobes and systems for the Air Force. Dr. Philbert received his PhD in neurochemistry and experimental neuropathology from London University. He was elected to the Institute of Medicine in 2012.

Kenneth R. Still is a retired US Navy Captain in the Medical Service Corps. He served as the senior director of safety and occupational health for the Commander of the US Pacific Fleet, Pearl Harbor, Hawaii, as well as the officer-in-charge of the Navy's Toxicology Research Laboratory Program in Dayton, Ohio. He is currently an adjunct assistant professor at Portland State University in the School of Community Health and participates in the Oregon Masters of Public Health program; he teaches both graduate and undergraduate courses in environmental health. Dr. Still is also the scientific director and senior toxicology consultant for Occupational Toxicology Associates, Inc., which provides consulting services for several Department of Defense programs. His research interests include human health risk assessment, exposure assessment, and regulatory and mechanistic toxicology. Dr. Still was a member the Academies Committee on Acute Exposure Guideline Levels and the Committee on Shipboard Hazard and Defense II, and currently serves on the Committee on Toxicology. He received his PhD in physiological ecology from Oklahoma State University. He is a fellow of the Academy of Toxicological Sciences and the American Industrial Hygiene Association, and is a certified industrial hygienist.

Joyce S. Tsuji is a principal scientist at Exponent, where she is involved in assessing health risks associated with substances in the environment, foods, consumer products, medical devices, and personal care products in the United States and internationally for industry, trade associations, the federal government, state agencies, municipalities, and private citizens. Her work has also involved environmental exposure studies and community programs involving health education and biomonitoring for populations potentially exposed to chemicals in the environment, including soil, water, and food-chain exposures. Dr. Tsuji is a board-certified toxicologist and a fellow of the Academy of Toxicological Sciences. She has served on expert committees for EPA, the US Army, and the state of Washington. She is currently a member of the Academies Board on Environmental Studies and Toxicology and the Committee on the Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry – Phase 1. Dr. Tsuji received a PhD focused on physiological ecology from the Department of Zoology at the University of Washington.

Carol S. Wood is a staff scientist in the Environmental Science Division of Oak Ridge National Laboratory. She has more than 20 years of experience as a toxicologist at Oak Ridge National Laboratory with extensive work in risk assessment for inhalation/pulmonary and oral toxicity of heavy metals and pesticides. She has worked on Acute Exposure Guideline Levels and Provisional Advisory

Levels, in which health-based exposure levels are developed for priority toxic chemicals. These projects often use toxicokinetic data and physiologically based pharmacokinetic models for extrapolation from animals to humans. Dr. Wood is on the Board of Directors of the American Board of Toxicology. At the request of the EPA, she wrote the guidance document "Standard Evaluation Procedure for Developmental Neurotoxicity Studies" and reviewed numerous submissions of testing and positive control neurotoxicity data. Her research experience and interests include developmental, reproductive, and neurotoxic outcomes from exposure to environmental contaminants. She is certified in general toxicology by the American Board of Toxicology. She served on the Institute of Medicine Committee on the Review of Clinical Guidance for the Care of Health Conditions Identified by the Camp Lejeune Legislation. Dr. Wood received her PhD in toxicology from Oregon State University.

Appendix B

Example Report Outlines for Future SMAC and SWEG Documents

OUTLINE FOR NEW CHEMICALS

I. Physical and Chemical Properties
II. Occurrence, Source, and Use on Spacecraft
III. Toxicokinetics
IV. Toxicodynamics and Mechanism of Action
V. Toxicity Summary
    a. Literature Search Strategy (summary of databases, dates, search terms, etc.)
    b. Acute Toxicity
        i. Human
        ii. Animal
    c. Short-Term Toxicity
        i. Human
        ii. Animal
    d. Subchronic Toxicity
        i. Human
        ii. Animal
    e. Chronic Toxicity
        i. Human
        ii. Animal
    f. Interaction with Other Chemicals
    g. Spaceflight Effects
VI. Rationale for Acceptable Concentrations
    a. Description of How Each SMAC/SWEG Was Derived (to include detailed justification of the selection of health end points, key studies, point of departure, and uncertainty factors)
    b. Exposure Standards Set by Other Organizations
VII. Research Recommendations

OUTLINE FOR UPDATING CHEMICAL GUIDELINES

I. Occurrence, Source, and Use on Spacecraft
II. Summary of Original Approach to Setting SMACs or SWEGs
III. New Data
    a. Literature Search Strategy (databases, dates, search terms, etc.)
    b. Toxicokinetics
    c. Toxicodynamics and Mechanism of Action
    d. Acute Toxicity
    e. Short-Term Toxicity
    f. Subchronic Toxicity
    g. Chronic Toxicity
    h. Interaction with Other Chemicals
    i. Spaceflight Effects
IV. Rationale for Revision to the Original SMACs or SWEGs
    a. Description of Revisions to Each SMAC/SWEG (to include detailed justification of the selection of health end points, key studies, point of departure, and uncertainty factors)
    b. Exposure Standards Set by Other Organizations
V. Research Recommendations