CHAPTER

5 A Nanoinformatics Approach to Safety, Health, Well-Being, and Productivity

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5.1 INTRODUCTION

As illustrated in Fig. 5.1, the context of nanoinformatics is that effective development and implementation of the imagined applications and benefits of nanotechnology requires the harnessing of information to support innovation and decision-making at the nexus of safety, health, well-being, and productivity; risk management; and emerging nanotechnology. There are many ways that this could be done, and as noted by risk-management expert Ed Zebroski (1991): "The method is not the message; [the message] is in the managerial frame of mind determined to make robust decisions."

Beginning with the creation of the community-based Nanoinformatics 2020 Roadmap (de la Iglesia et al., 2011) and expanding through experience such as working at the nexus of nanotechnology and radiation safety (Hoover et al., 2015), the working definition of nanoinformatics as illustrated in Fig. 5.2 has evolved to be

- Setting mission objectives for safety, health, well-being, and productivity related to the development and application of nanoscale science, engineering, and technology;
- Determining which information is relevant to meeting the safety, health, well-being, and productivity objectives of the nanoscale science, engineering, and technology community;

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FIGURE 5.1

Context of the nanoinformatics approach to innovation and decision-making at the nexus of safety, health, well-being, and productivity; risk management; and emerging nanotechnology.

Adapted from Hoover, M.D., Myers, D.S., Cash, L.J., Guilmette, R.A., Kreyling, W.G., Oberdörster, G., Smith, R., Cassata, J.R., Boecker, B.B., Grissom, M.P., 2015. Application of an informatics-based decision-making framework and process to the assessment of radiation safety in nanotechnology. Health Physics 108 (2), 179–194.

- Developing and implementing effective mechanisms for collecting, validating, storing, sharing, analyzing, modeling, and applying the information;
- Confirming that appropriate decisions were made and that desired mission outcomes were achieved as a result of that information; and finally
- Conveying experience to the broader community, contributing to generalized knowledge, and updating, guidance, standards and training.

As illustrated in Fig. 5.3, the diverse individuals who engage in nanoinformatics can be viewed as fitting across four categories of roles and responsibilities for nanoinformatics methods and data:

- Customers (who need either the methods to create the data, the data itself, or both, and who specify the scientific applications and characterization methods and data needs for their intended purposes),
- Creators (who develop relevant and reliable methods and data to meet the needs of customers in the nanotechnology community),
- Curators (who maintain and ensure the quality of the methods and associated data), and

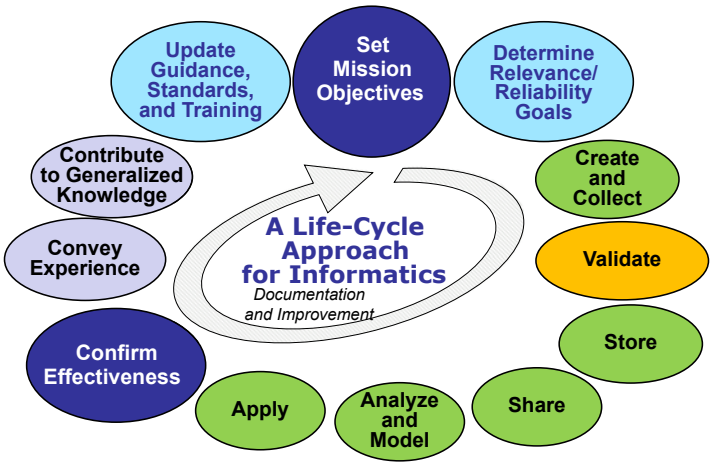


FIGURE 5.2

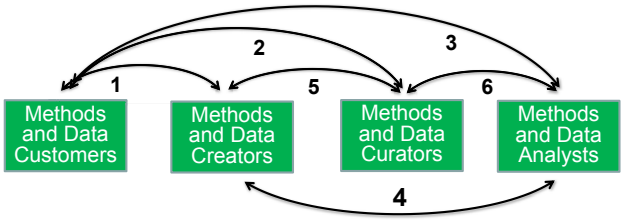
Illustration of the science and practice of nanoinformatics as a life cycle process. The steps are presented in order and a variety of shapes are used to suggest important relationships among the steps, including beginning by setting mission objectives and then later confirming how effective the use of that information has been to achieve those objectives; determining relevance and reliability goals for the information and then later reflecting details of those criteria in, guidance, standards and training; carrying out the learning portion of the cycle from information creation and collection through application; and validating the information during the learning portion and then later conveying results of the learning experience to the community and interpreting that information to contribute to generalized knowledge.

- Analysts (who develop and apply methods and models for data analysis and interpretation that are consistent with the quality and quantity of the data and that meet customers' needs).

In some instances, the same individuals perform all four roles. More often, many individuals must interact with their roles and responsibilities extending over significant distances, organizations, and time. Success requires that communication be effective across each of the 12 links (i.e., in both directions across each of the six interfaces) that exist among the various customers, creators, curators, and analysts.

As illustrated in Fig. 5.4, foundational pillars of connected, protected, and respected leaders, cultures, and systems must be built and sustained to successfully understand, communicate, and manage protection from risks in our increasingly interconnected world. The goal of an informatics approach to safety and success in any setting can be viewed as

- making it easier for everyone to *get the right things done right*
- by building and sustaining *connected, protected, and respected communities*



	Set Mission Objectives	Determine Relevance	Collect	Validate	Store	Share	Analyze and Model	Apply	Confirm Effectiveness	Convey Experience	Generalize	Update Guidance
Customers	X	X						X	X	X	X	X
Creators		X	X	X					X			X
Curators		X		X	X	X			X			X
Analysts		X		X			X		X		X	X

FIGURE 5.3

An informatics view of the communication interfaces, roles, and responsibilities for methods and data customers, creators, curators, and analysts.

Adapted from Hoover, M.D., Myers, D.S., Cash, L.J., Guilmette, R.A., Kreyling, W.G., Oberdörster, G., Smith, R., Cassata, J.R., Boecker, B.B., Grissom, M.P., 2015. Application of an informatics-based decision-making framework and process to the assessment of radiation safety in nanotechnology. Health Physics 108 (2), 179–194.

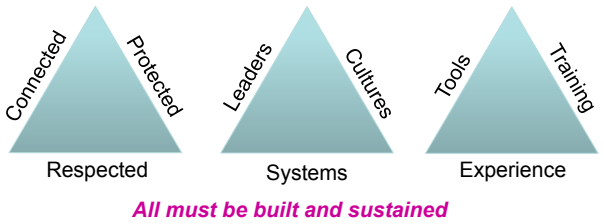


FIGURE 5.4

Essential components for connected, protected, respected communities of leaders, cultures, and systems with all the tools, training, and experience needed to control and confirm protection from risks in any setting.

- of *leaders, cultures, and systems*
- that are equipped with all the appropriate *tools, training, and experience*
- needed *to anticipate and recognize hazards, evaluate exposures, and control and confirm protection from risks* to safety, health, well-being, and productivity
- in all the places we *live, learn, work, and play.*

The information, tools, and examples in the following sections of this chapter support the application of the nanoinformatics approach to important aspects of

communicating among audiences with differing levels of expertise, using a framework and process for anticipating and recognizing hazards, evaluating exposures, and controlling and confirming protection from risks. The work of the broad nanotechnology community to develop and apply effective nanoinformatics principles and practices to understand, communicate, and manage risks is evidence of a commitment to engaging the community to improve safety, health, well-being, and productivity, especially through ensuring the efficacy of products and the safe applications of nanotechnology as well as other emerging technologies. The communal work in this multisectoral, interdisciplinary field to harmonize data formats and create tools for data sharing has been a successful experiment in collaboration and trust, generating a seed ontology (http://www.nano-ontology.org), shared data formats (Thomas et al., 2011; Baker et al., 2013), a collaborative framework for data sharing (Harper et al., 2013), and state of the field assessments of data integration and curation practices (Powers et al., 2015; Hendren et al., 2015; Marchese-Robinson et al., 2016; Karcher et al., 2018). The development of a coherent set of nanoinformatics principles has evolved over more than a decade.

Many of the key details presented below about the nanoinformatics framework and process and its application have been drawn directly from a chapter on confirming critical terminology concepts and context for clear communication (Hoover et al., 2014) published in the *Encyclopedia of Toxicology* (Wexler, 2014). As noted in that chapter, the framework and supporting process were developed to be generally applicable to meeting any objective. As described here, they can be continuously applied to any aspects of safety, health, well-being, and productivity for nanotechnology.

5.2 COMPONENTS OF INFORMATICS-BASED DECISION MAKING

5.2.1 A COMMUNICATION AND EDUCATION MESSAGE AND AUDIENCE-PLANNING MATRIX

The practice of nanoinformatics begins with a clear understanding of our community and our audiences. The communication and education message and audience-planning matrix illustrated in Fig. 5.5 can be used to identify, build, and sustain relevant and reliable leaders, cultures, and systems within key stakeholder groups.

The communication and education process can be tailored by each stakeholder group to understand their roles, responsibilities, needs, and potential contributions and to engage their collaboration. This process applies for any situation of interest.

The example stakeholder list originated from the point of view of advancing occupational safety, health, well-being, and productivity in any context. The list

	Workers	Health and safety practitioners	Managers	Policy makers and regulators	Equipment and facility providers	Materials suppliers	Financiers	Insurers	Legal community	Researchers	Educators	Students	Emergency Responders	Media	Consumers	Society
Literacy and Critical Thinking Skills																
Real Life Examples																
Understanding (not rote application)																
Continuous Improvement																
Modeling and Sharing																
Assessment																

FIGURE 5.5

A communication and education message and audience-planning matrix of general applicability. Specific messaging and actions in each element of the matrix must be based on what knowledge and understanding each stakeholder needs and what knowledge and understanding each stakeholder can provide.

From Hoover, M.D., Cash, L.J., Mathews, S.M., Feitshans, I.L., Iskander, J., Harper, S.L., 2014. 'Toxic' and 'nontoxic': confirming critical terminology concepts and context for clear communication. In: Wexler, P., (Ed.), Encyclopedia of Toxicology, vol. 4, third ed. Elsevier, Oxford, pp. 610–616.

begins with workers because workers are the first individuals to come in contact with newly developed materials. Frequently overlooked subgroups in the workplace include maintenance, custodial, security, contractor, and volunteer workers, as well as visitors. The list extends through health and safety practitioners, managers; policy-makers and regulators; equipment and facility providers; materials suppliers; financiers, insurers, and the legal community; researchers, educators, and students; emergency responders; the media; and consumers and society in general. Areas that involve substantial interactions across stakeholder groups include assessing legal issues for designing an effective regulatory compliance program or addressing the global health impacts of nanotechnology (Feitshans, 2013, 2018). The list can be expanded or contracted and serves to incorporate relationships of safety, health, well-being, and productivity from the earliest steps of planning, design, and outset of any activity, facility, or system, rather than as an afterthought.

Most individuals fall into more than one category, with needs and abilities to obtain or provide information that may be similar or different from those of other stakeholders. For example, a health researcher who also serves as a health and safety practitioner must ensure their own protection as well as protection of their students and colleagues in a research setting. The information needed to identify, plan, fund, and safely conduct their work may be the same or different from that needed to

inform a vendor of their equipment and system needs, obtain study materials from qualified suppliers, or educate their target audiences about their research results.

The communication and education attributes in the row aspect of the planning matrix were adapted from the American Statistical Association *Guidelines for Assessment and Instruction in Statistics Education Report* (Franklin et al., 2007). They are

1. emphasize literacy and build, sustain, and apply critical thinking skills;
2. develop and use real-life data examples;
3. stress conceptual understanding rather than mere application of procedures;
4. foster continuous improvement and active discussions;
5. use technology for developing conceptual understanding and for analyzing and sharing information (e.g., modeling and simulation, databases, wikis, etc.);
6. use assessments to evaluate and improve the efficacy and impact of these activities.

Stakeholder-specific communication and education for each element of the matrix requires dialogue among the stakeholders and tailoring of message development based on (1) what knowledge and insights each stakeholder needs and (2) what knowledge and insights each stakeholder possesses and can provide. Each stakeholder group can discuss and assess its past, current, and future communication needs within its own group and externally with other groups.

5.2.2 THE ANTICIPATE, RECOGNIZE, EVALUATE, CONTROL, AND CONFIRM DECISION-MAKING FRAMEWORK AND PROCESS

The decision-making framework of *anticipate, recognize, evaluate, control, and confirm* (ARECC) illustrated in Fig. 5.6 arises from the field of industrial hygiene (e.g., Brandt, 2010; Hoover et al., 2011; Laszcz-Davis et al., 2014; Jahn et al., 2015) and supports hazard-, exposure-, and risk-informed decision-making in any endeavor. A version of the Fig. 5.6 graphic appears as the first illustration in the authoritative industrial hygiene reference book *A Strategy for Assessing and Managing Occupational Exposures* (Jahn et al., 2015). The framework began many decades ago as *recognize, evaluate, and control; and it* was strengthened to *anticipate, recognize, evaluate, and control* in 1994, when then-president of the American Industrial Hygiene Association (AIHA) Harry Ettinger added the *anticipate* step to formally encourage the worker protection community to proactively apply its growing body of knowledge and experience; and the framework was finally expanded to ARECC (Hoover et al., 2011) to confirm that all steps in the decision-making framework were being effectively applied and that the desired outcomes were being achieved. Overall confirmation of the adequacy of decision-making for risk management can include evaluation of results from occupational epidemiological studies. Confirmation of training, documentation, and continuous improvement of the entire decision-making process must be carried out to ensure that all steps are scientifically grounded and appropriately applied.

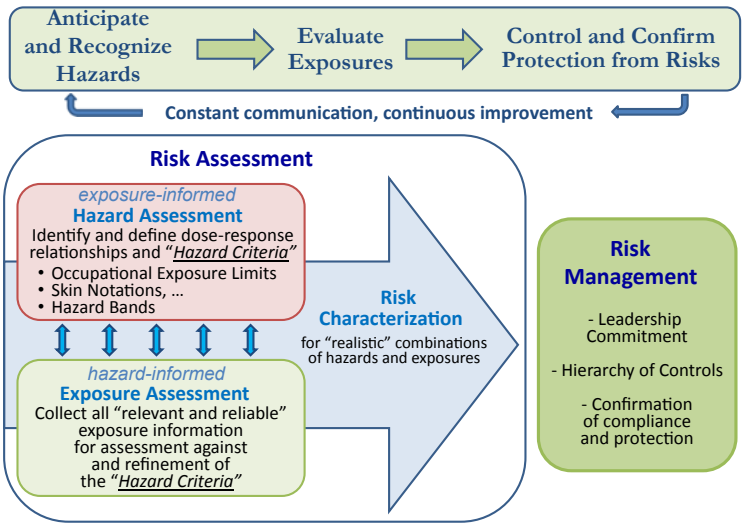


FIGURE 5.6

The anticipate, recognize, evaluate, control, and confirm (ARECC) framework and process for hazard-informed, exposure-informed, and risk-informed decision-making to confirm protection of safety, health, well-being, and productivity.

Adapted from Hoover, M.D., Armstrong, T., Blodgett, T., Fleeger, A.K., Logan, P.W., McArthur, B., Middendorf, P.J., 2011. Confirming our industrial hygiene decision-making framework. The Synergist 22 (1), 10.

Application of ARECC in the current context is intended to enable the nanoscale science and related communities to

- *anticipate* that myriad nanoenabled applications, processes, nanomaterials, and nanoparticles are already present or may become present in almost all activities;
- *recognize* specific situations where environmental and worker safety, health, well-being, and productivity may be affected;
- *evaluate* how radiation protection practices may need to be altered to improve protection;
- *control* information, assumptions, interpretations, and conclusions to implement scientifically sound decisions and actions; and
- *confirm* that desired protection outcomes have been achieved.

The framework recognizes the essential contributions of leaders, cultures, and systems to achieving success. When failures to protect people and the environment from risks have occurred, root causes of those failures can be traced to shortcomings or breakdowns in one or more aspects of the prevailing leaders, cultures, and systems. Note that the ARECC elements of training, documentation, and improvement shown in Fig. 5.6 support the premise that relevant and reliable leaders, cultures, and systems must be built and sustained. In addition, inclusion of the caveat "over which we have influence" recognizes that relevant and reliable

leaders, cultures, and systems can only exist to the extent that they can be influenced in positive and meaningful ways. Aspects of the decision-making framework and process related to building and sustaining relevant and reliable leaders, cultures, and systems can be particularly important when disparate technologies or activities are converging.

The implementation of ARECC involves conducting risk assessment and applying risk management. During the risk assessment phase, the details of existing or potential hazards and exposures are assessed to characterize risks. The hazard identification/dose–response/exposure assessment/risk assessment approach mirrors the process that was formulated by the National Academy of Sciences/National Research Council (NAS/NRC, 1983, 2009). Schulte et al. (2014) noted the interrelated criteria of hazard identification/exposure assessment/risk assessment/risk management/fostering of benefits for responsible development of nanotechnology. Schulte et al. (2016) also noted significant examples of progress in the fields of toxicology, metrology, exposure assessment, engineering controls, personal protective equipment (PPE), risk assessment, risk management, medical surveillance, and epidemiology for protection of nanotechnology workers. As emphasized in Fig. 5.6, strong interactions are needed between the hazard assessment and exposure assessment activities. *Exposure-informed hazard assessment* ensures that realistic information about actual workplace exposure compositions, concentrations, and conditions is factored into any laboratory-based studies of health effects that are conducted. *Hazard-informed exposure assessment* ensures that the relevant exposures are assessed in the appropriate locations and at the appropriate times. Identifying and defining dose–response relationships for exposures to hazards allow for the establishment of occupational exposure limits, hazard criteria for concerns such as exposures to skin, and the grouping of materials into hazard bands that can be similarly controlled. The risk-management portion of the ARECC framework and process emphasizes leadership commitment to the safety mission, application of the hierarchy of controls, and confirmation that the process steps are being followed and that protection of safety, health, well-being, and productivity is being achieved.

5.2.3 THE HIERARCHY OF CONTROLS

The hierarchy of controls is traditionally depicted as a pyramid of control components beginning at the top with elimination of the hazard as the most effective control, followed by substitution of a less hazardous option, followed by engineering controls, followed by administrative and work practice controls, and concluding with use of PPE as the least effective control at the bottom. Fig. 5.7 depicts a newly configured interrelated elements depiction of the pyramid that emphasizes the interactivity and sustainability aspects of the various risk control activities, along with the manner in which it can be used to assess the past, current, or future levels of protection.

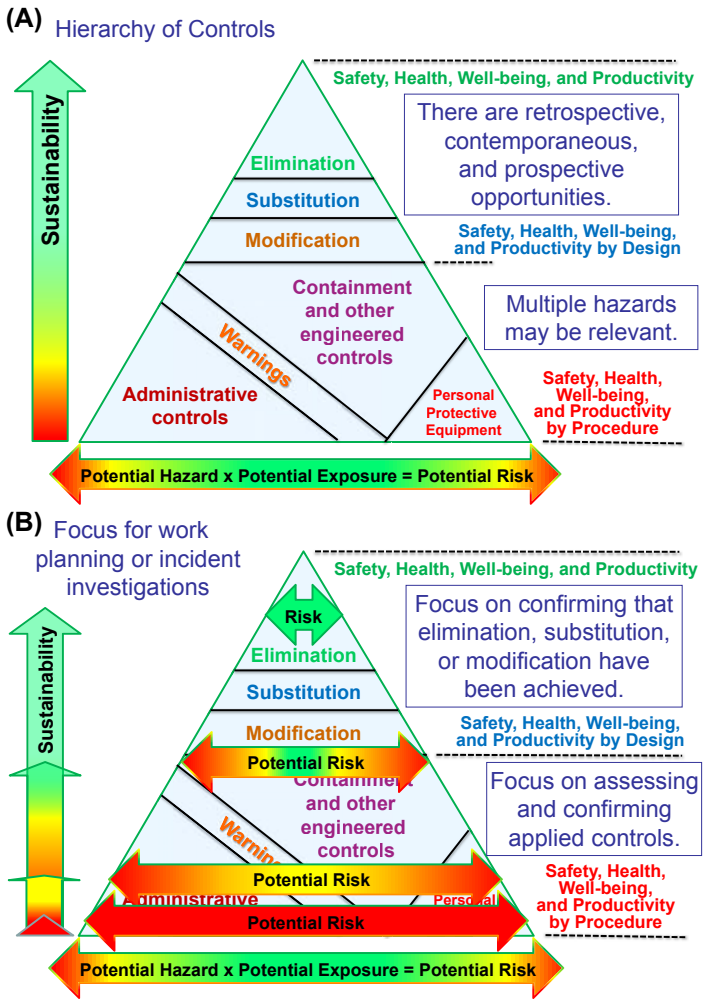


FIGURE 5.7

Depiction of the hierarchy of controls as a pyramid of interrelated components that conveys (A) how various levels of control are associated with different levels of potential risk and sustainability and (B) how retrospective investigations of past incidents or contemporaneous or prospective job safety analyses and planning can be informed by knowledge about the types of controls being applied.

As shown in Fig. 5.7A, the components depicted in the interrelated hierarchy are

- *Elimination* of the presence or magnitude of the hazard (not always possible if the material or condition is essential to the activity objectives but sometimes possible in the case of objectives that can be achieved by methods such as computer simulation),

- *Substitution* of a less hazardous material or procedure (sometimes possible, such as through the use of materially similar surrogates or the use of less dispersible materials or less energetic processes; however, it is prudent to remember that "regrettable substitution" is a term that applies to situations in which assumptions about the risk-reduction advantages of the substitution turned out to be wrong; recent examples noted by Zimmerman and Anastas (2015) are the substitution of bisphenol S for bisphenol A in plastics, and the substitution of alpha-diketone for diacetyl in butter flavorings),
- *Modification* of the material or procedure to reduce hazards or exposures (sometimes considered a subset of the substitution option but explicitly considered here to mean that the efficacy of the modification for the situation at hand must be confirmed by the user),
- *Engineering controls* to prevent exposures (includes a variety of physical containment and ventilation strategies),
- *Warnings* to indicate the need for and status of control (explicitly considered here to be a distinct hierarchy option to emphasize the growing capabilities and availability of real time sensors and monitors; whereas in other systems, warnings are sometimes considered part of engineered controls and sometimes part of administrative controls),
- *Administrative and work procedures* to prevent exposures and confirm protection (an approach that relies highly on training and compliance, and includes medical screening, surveillance, and epidemiological studies of potentially exposed individuals), and finally, as the last barrier to exposure,
- *PPE* (including respiratory protection).

Fig. 5.7B illustrates the advantage of the revised depiction of the hierarchy because of the manner in which the depiction of the interrelated elements can readily be used to guide retrospective, contemporaneous, or prospective assessments of work activities that involve different combinations of hazards, exposures, controls, and resulting risks. For example, if a hazard was thought to have been eliminated from a process, then initial evaluations can focus on confirmation of material inventories and process knowledge. Similarly, control situations that rely heavily on engineered controls, warnings, work practices, or use of PPE can focus on confirmation of whether those controls were actually in place and properly applied. In addition, other hazards may also be present such as heat stress, slips trips and falls, struck-by injuries, toxic metals, toxic gases, electrical shock, lasers, shift work, and fatigue. If multiple hazards are present in a work activity, the status of the hierarchy of controls can be assessed for each hazard, and a worst-first, all-hazards approach can be used to prioritize actions to ensure protection from risks. Ideally, as recommended in the American National Standard for Prevention through Design (ANSI/ASSE, 2011) the hierarchy will be used to guide the design of work in a manner that will prevent the presence of hazards, exposures, and resulting risks.

5.2.4 A SET OF CLEAR COMMUNICATION ASSESSMENT CRITERIA

Fig. 5.8 uses the word CLEAR as an acronym to convey a set of assessment criteria that flow "from the ground up" in a reverse order pyramid configuration (relevant, accurate, ethical, logical, and concise) to help readers and writers ARECC effective communication in general, and, as described here, to understand and manage safety issues that pertain specifically to nanotechnology. The details of the CLEAR communication assessment criteria were originally developed to guide a formal scientific review process for physicians and other health-care professionals (Iskander, 2012; Iskander et al., 2017). A variety of word choices were considered for the anagram and the choice of individual words and their meanings in Fig. 5.8 acronym can be adjusted to support the needs and concerns of any reader, writer, reviewer, or practitioner.

Relevant is shorthand for ensuring that the communication is relevant to the needs of the reader and relevant to the mission of the writer. Relevance is the foundational criterion for CLEAR communication. Readers are responsible for assessing and ensuring that the content of the presentation is relevant to the details of their situation (e.g., type and form of hazard and nature and magnitude of exposure), including issues of any potential bias or conflicting or competing interests on the part of the writer. Similarly, writers need to assess and ensure that their products are fundamentally relevant to their mission and expertise and tailored to the needs of their intended audience.

Step	Attribute
00	Establish CLEAR objectives
0	Address uncertainty
1	Address false positive conclusions
2	Address false negative conclusions
3	Apply appropriate decision levels
4	Apply appropriate evaluation methods
5	Differentiate correlation from causation
6	Apply appropriate extrapolations
7	Develop adequate documentation
8	Address mishap or misconduct

FIGURE 5.8

A set of CLEAR communication assessment criteria and the attributes of 10 critical steps than can be taken to avoid flaws in decision-making for understanding, communicating, and managing risks.

Adapted from Hoover, M.D., Cash, L.J., Mathews, S.M., Feitshans, I.L., Iskander, J., Harper, S.L., 2014. 'Toxic' and 'nontoxic': confirming critical terminology concepts and context for clear communication. In: Wexler, P., (Ed.), Encyclopedia of Toxicology, vol. 4, third ed. Elsevier, Oxford, pp. 610–616.

Accurate is shorthand for matching the certainty of presentation to the reliability of supporting information. For issues that are not yet well understood, an introductory informational pamphlet or web posting might highlight a growing issue of concern, without implying more than is justified by the current state of knowledge. For issues that have been extensively studied and understood according to rigorous scientific procedures, the degree of certainty in the presentation might be justifiably higher.

Ethical is shorthand for ensuring that all ethical, legal, and social implications of the work are on a solid footing. By its very nature, work in the realm of health and safety must not only be conducted in a manner that is thoroughly ethical and legal but it must also be readily apparent that such is the case. *Informed consent* is a well-recognized tenet of research ethics.

Logical is shorthand for ensuring that the intended message is organized and conveyed in a manner that is not only scientific and technically defensible but also fundamentally understandable. Logic can extend to issues of plain language, and use of language that is tailored to the intended audience.

Concise, the crowning criteria, does not necessarily mean "short" but focuses on ensuring that any extraneous materials are rejected or moved to other communications so that the core message of the communication can be readily understood and applied. Note that application of the concise criteria supports the creation of comprehensive resources such as encyclopedias, which are not short, but whose individual components are designed to address and meet specific reader needs.

For example, in the case of nanotechnology, an informatics goal is to identify and assemble a useable body of knowledge from authoritative sources such as the National Institute for Occupational Safety and Health (e.g., NIOSH, 2009, 2011, 2013, 2018a,b,c), the AIHA (e.g., Kulinowski and Lippy, 2011a; Hoover and Rickabaugh, 2014; Barrie et al., 2017), and the AIHA Nanotechnology Working Group (AIHA, 2015a,b). The National Council on Radiation Protection and Measurements has developed guidance on the radiation safety aspects of nanotechnology (NCRP, 2017). Additional resources include the GoodNanoGuide (https://nanohub.org/groups/gng); the National Nanotechnology Initiative signature initiative on Nanotechnology Knowledge Infrastructure—Enabling National Leadership in Sustainable Design, and the signature initiative on Nanotechnology for Sensors and Sensors for Nanotechnology: Improving and Protecting Health, Safety, and the Environment (http://www.nano.gov/signatureinitiatives); the Nanomaterial Registry (https://www.nanomaterialregistry.org); the Nanotechnology Committee of the Health Physics Society (http://hps.org/aboutthesociety/organization/committees/committee66.html); and the Nanotechnology Institute within the Institute of Environmental Sciences and Technology (http://www.iest.org/Nanotechnology-Institute).

5.2.5 STEPS TO AVOID FLAWS IN DECISION-MAKING

Fig. 5.8 also lists 10 steps that can be taken to avoid critical flaws that can affect the quality of CLEAR communication and the associated decision-making.

Information customers, creators, curators, and analysts can be aware of the attributes of these steps and can apply each of these steps to avoid potential flaws in decision-making. At the 00 Level, before any other actions are taken, the most fundamental flaw to be avoided is the lack of CLEAR objectives, based on the communication assessment criteria described above. In any situation, objectives should include protection of workers, protection of the environment, assurance of product or process quality, preparation for emergencies, and demonstration of compliance according to regulatory or other requirements. Attention to avoiding flaws in setting of CLEAR objectives is followed at the 0 Level by the need to address uncertainty, which affects all aspects of study design and conduct. Steps at Levels 1 and 2 correspond to the essential and widely recognized need to address Type 1 and Type 2 statistical errors (jumping to a false-positive conclusion or making a false-negative conclusion). Level 3 addresses the need to avoid the use of an inappropriate decision level, such as planning an action that has a 5% chance of failure (1 in 20 events) when a failure rate of less than 1 in 1000 is needed to protect involved individuals. Level 4 addresses the need to avoid the flaw of using an inappropriate evaluation method, such as only testing the toxicity of a substance by ingestion when the actual route of administration includes inhalation. Level 5 addresses the need to avoid the flaw of equating correlation with causation, such as when the mode of toxic action may be associated with a contaminant in a test material, rather than with the substance thought to have been tested. Level 6 seeks to avoid the flaw of inappropriate extrapolation of information to a situation for which the test conditions are either irrelevant, unreliable, or both. Level 7 addresses the flaw of inadequate documentation, which can be particularly important in legal or regulatory settings. Level 8 addresses the reality that experiments, data, or information can sometimes be inadvertently miscollected or misrecorded or that someone may deliberately falsify results.

5.2.6 SEVEN PARTS FOR GETTING THE RIGHT THINGS DONE RIGHT

Fig. 5.9 presents "seven parts for getting the right things done right" in a manner that emphasizes the importance of the objective-setting step in the informatics-based decision-making framework and process. The details of the seven parts for getting the right things done right are conveyed in a humorous manner, but their intent is serious. Success in any endeavor requires more than just doing things. Success requires getting the right things done right. CLEAR thinking at the objectives-setting step of the decision-making process is essential because once intended actions have been identified and have begun, it can be difficult to reassess the extent to which those actions continue to represent the right things that need to be done, as well as the extent to which those right things are being done right. The process of deciding what to do is separate and different from the process of doing something. A timeout might be needed to safely disengage and reassess what needs to be done next. In other words, "don't begin thinking about whether you should be walking across the tightrope while you are in the middle of walking across the tightrope."

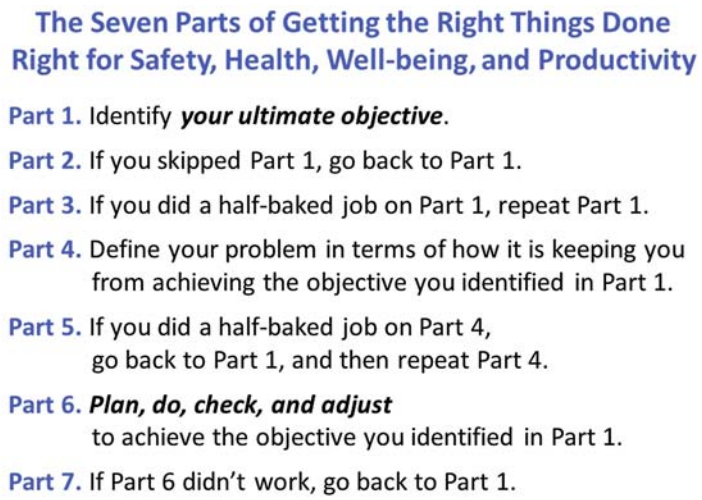


FIGURE 5.9

The seven parts for getting the right things done right for safety, health, well-being, and productivity. An endorsement of the value of effectively understanding, communicating, and managing objectives and actions for success.

5.3 TOOLS FOR ASSESSING INFORMATION RELEVANCE AND RELIABILITY

5.3.1 RELEVANCE VERSUS RELIABILITY ASSIGNMENT

Fig. 5.10A (the first of a suite of six quadrant tools for assessing information) presents a triage process for readers and other data customers to conduct due diligence and to assign information according to its relevance and reliability for a specific application.

Information assigned to the "fit-for-purpose" (green) category can be given priority for interpretation and action. Information that is not fit for purpose should be assigned to the red or yellow categories. Information developed for ecotoxicology may be highly relevant and sufficiently reliable for its intended use but irrelevant to questions in human toxicology. Some information may appear to address a relevant question but may only be of a preliminary nature and therefore unreliable. The details are important. As new work is proposed, writers and researchers can use the relevance-versus-reliability assignment process to guide fit-for-purpose development of new information. In the Nanotechnology Knowledge Infrastructure signature initiative draft discussion on data readiness levels, a method analogous to Technology Readiness Levels was proposed to assess and convey information about the quality and maturity of data for a given application (NNI, 2013). The proposed data readiness levels included

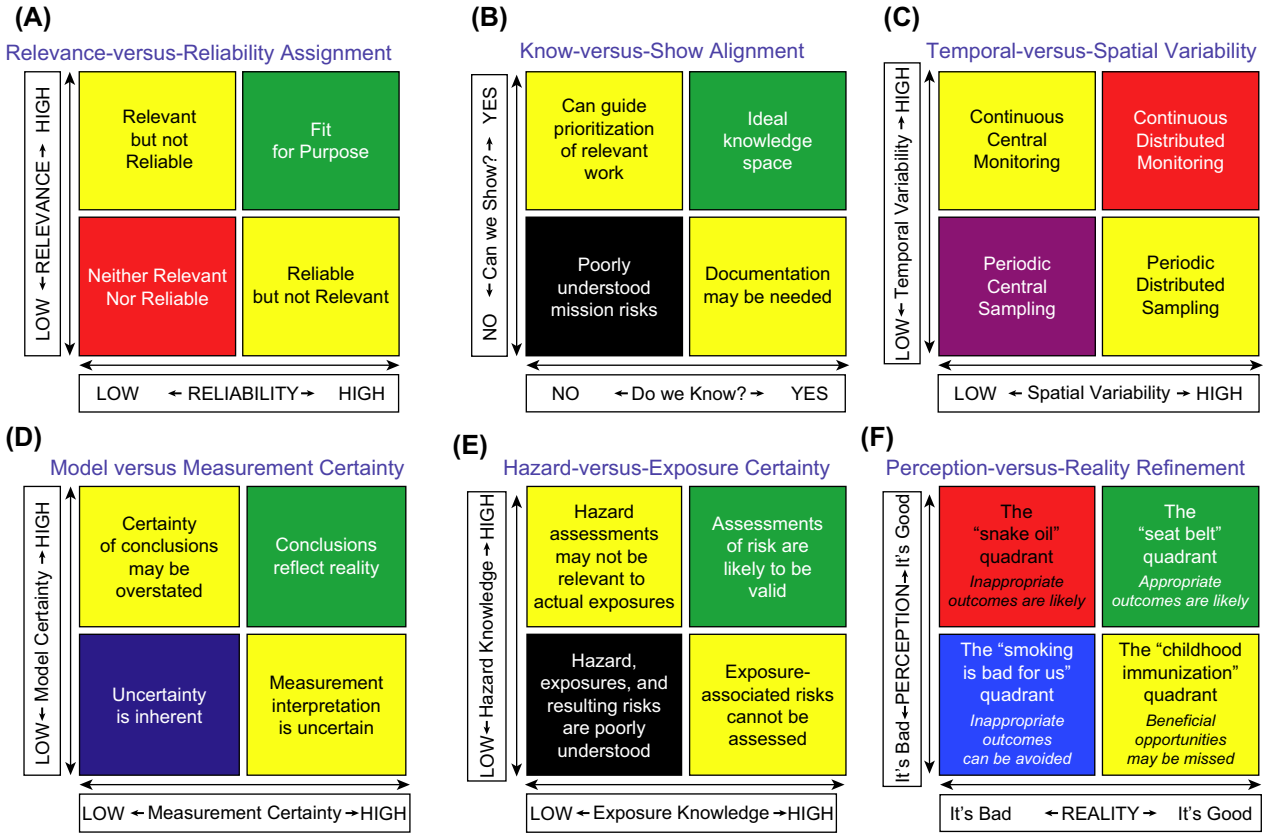


FIGURE 5.10

Suite of quadrant tools to (A) assign relevance-versus-reliability, (B) align know-versus-show, (C) adapt to temporal-versus-spatial variability, (D) interpret model-versus-measurement certainty, (E) interpret exposure-versus-hazard certainty, and (F) refine perception-versus-reality aspects of information.

Adapted from Hoover, M.D., Cash, L.J., Mathews, S.M., Feitshans, I.L., Iskander, J., Harper, S.L., 2014. 'Toxic" and 'nontoxic': confirming critical terminology concepts and context for clear communication. In: Wexler, P., (Ed.), Encyclopedia of Toxicology, vol. 4, third ed. Elsevier, Oxford, pp. 610–616 and Hoover, M.D., Myers, D.S., Cash, L.J., Guilmette, R.A., Kreyling, W.G., Oberdörster, G., Smith, R., Cassata, J.R., Boecker, B.B., Grissom, M.P., 2015. Application of an informatics-based decision-making framework and process to the assessment of radiation safety in nanotechnology. Health Physics 108 (2), 179–194.

1. Invalid data that lack accuracy or documentation,
2. Raw or unscaled data that have not yet been converted to appropriate physical units,
3. Scaled data that require replication and the assignment of uncertainty,
4. Data that have defined precision and uncertainty based on duplicate measurements but that have not yet been confirmed by independent observations,
5. Data that have precision confirmed by independent observations but that have not yet been related to the larger body of scientific knowledge,
6. Data that can been related to the larger body of scientific knowledge but that have measurement uncertainty too large for the designed data standards,
7. Data with uncertainty that have been defined at a known percentage and that are acceptable for the intended application.

The proposed data readiness levels are augmented with metadata qualifiers that enable further assessment, reproduction, or use of the data by others.

5.3.2 KNOW-VERSUS-SHOW ALIGNMENT

Fig. 5.10B presents a complementary process for aligning a need/ability to know something versus the need/ability to show it. Risk-management expert Stan Kaplan (1991) has noted that "If money is being spent to reduce an already minuscule risk, while larger risks are going unaddressed, that is not only foolish; it is in effect an unsafe act." Thus, the know-versus-show process addresses the importance of the intelligent allocation of resources to understand and document risk-related information.

It would be ideal if all information *relevant* to a concern could be both known and shown (and therefore assigned to the green quadrant). Additionally, it would be ideal to clearly establish what information falls into the "known but not shown" or "neither known nor shown" yellow quadrants. Medical studies conducted according to good laboratory practice rightly require extensive documentation such as checklists, signatures, photography, etc., to "show" what was done. Knowing what others have done can avoid duplication of work. Thus, establishing what is in the "it can be shown that this is not known" black quadrant has value for guiding the prioritization of relevant work. Better sharing of nanotechnology-related information can improve the efficiency and effectiveness of efforts to improve safety, health, well-being, and productivity. Knowing and being able to show through measurements and defensible documentation that an action or condition is present (i.e., that we know we have a problem) does not necessarily mean that an appropriate interpretation or response to that action or condition is available or even possible (i.e., that we know how to solve the problem).

5.3.3 TEMPORAL-VERSUS-SPATIAL VARIABILITY

Fig. 5.10C (an addition to the original suite of quadrant tools presented in the Encyclopedia chapter) addresses the need to adapt the frequencies and locations of hazard and exposure assessments to the temporal and spatial variability of activities in the workplace or environment. Hazard and exposure assessment responses to different situations can range from the purple quadrant of periodic central sampling to the red quadrant of continuous distributed monitoring or to combinations of both in the yellow quadrants. Continuous monitoring may be needed if conditions vary or have significant potential to vary. Considerations about when and where things are the same or different also apply to the determination of the performance characteristics of nanomaterials and nanoformulated products. Attention to the life cycle of nanomaterials and nanoenabled products can guide how temporal and spatial variability issues will need to be addressed.

5.3.4 MODEL-VERSUS-MEASUREMENT CERTAINTY

Fig. 5.10D (also an addition to the original suite of quadrant tools) addresses relationships among the certainty of a measurement (such as determination of the airborne particle size distribution of a radioactive nanomaterial), the certainty of the model in which the measurement is used (such as a workplace or atmospheric dispersion model, a model of deposition in the respiratory tract, or a model of potential health effects), and the certainty of associated conclusions. Uncertainty is inherent (the blue quadrant) when both the models and the data they employ are uncertain. Using measurements of low certainty in models that require input data of high certainty (the upper left yellow quadrant) can result in overstating the certainty of a particular conclusion. Investing in collection of high-certainty measurements, when only models of limited certainty are available (the lower right yellow quadrant) can result in conclusions that are less reliable than may ultimately be possible. Intelligent decisions arising from the green quadrant require investment in the development of both defensible measurements and defensible models to interpret those measurements. At any time in the risk assessment process for any activity, the certainty of conclusions should be appropriately established.

5.3.5 HAZARD-VERSUS-EXPOSURE CERTAINTY

Fig. 5.10E (also an addition to the original suite of quadrant tools) illustrates how the validity of risk assessment is influenced by the degree to which the nature of hazards and exposures are known or unknown. When neither the nature of the hazard nor the nature of the exposure is known (the black quadrant), then risks cannot be reliably assessed. Increasing knowledge about a hazard without increasing knowledge of the actual exposure conditions (the upper left yellow quadrant) means that hazard assessments may not be relevant to actual exposures. Increasing the knowledge

about exposures in the absence of knowledge about the associated hazards (the lower right yellow quadrant) also means that risks cannot adequately be assessed. In reporting insights from their experiences in the exposure assessment and inhalation toxicology of carbon nanotubes, Erdely et al. (2016) recommended the use of a strong integrated approach between exposure assessment and the design and conduct of toxicity testing. The ideal state of knowledge is in the upper right green quadrant where exposure-informed hazard assessment and hazard-informed exposure assessment have enabled assessments of risk that are likely to be valid. Achieving knowledge of the risk-relevant details of hazards and exposures enables hazard- and exposure-informed risk assessment and enables risk-informed decision-making and actions.

5.3.6 PERCEPTION-VERSUS-REALITY REFINEMENT

Fig. 5.10F illustrates the need to refine perceptions when the perception of what is bad or good, toxic or nontoxic, safe or unsafe does not match reality. When perception matches reality, then engaging in actions associated with what is depicted in green as the "seat belt" quadrant makes it more likely that good outcomes will occur. Similarly, avoiding actions associated with the so-called "smoking is bad for us" quadrant that is shown in blue enables bad outcomes to be avoided. However, correctly perceiving an action as being good or bad does not ensure that the action is engaged in appropriately or avoided. For example, seat belts are good for us and we generally perceive them to be good for us, but some people still do not use seat belts. Similarly, smoking is bad for us, and we generally perceive smoking to be bad for us, but some people still smoke.

Informed action may be needed to refine perceptions in a manner that moves misperceived situations out of the red "snake-oil" quadrant (where inappropriate outcomes are likely because a bad action is perceived to be good) and out of the yellow "childhood immunization" quadrant (where beneficial opportunities may be missed because a good action is perceived to be bad). Thus, our ability to advance safety, health, well-being, and productivity depends on our ability to understand and refine the match between perception and reality and ultimately to improve appropriate compliance. Given that nanotechnology is an emerging technology there are perception questions about the inherent safety of nanomaterials and their applications, and mismatches of perception and reality have long plagued fields involving radiation and radioactive materials.

5.3.7 INTRINSIC PROPERTIES VERSUS CONDITIONAL BEHAVIORS

Throughout the process of developing relevant and reliable information for nanotechnology safety, health, well-being, and productivity, an essential distinction can be made between the intrinsic properties of materials and the conditional behavior of those materials in specific settings. Figs. 5.11 and 5.12 illustrate that

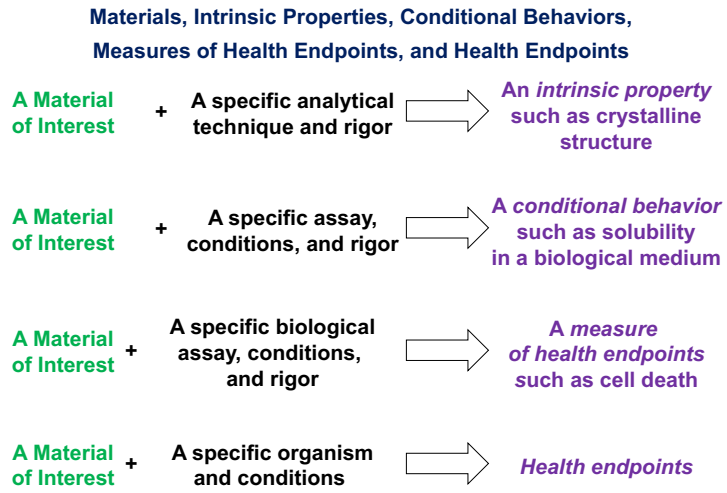


FIGURE 5.11

Intrinsic properties and conditional behavior issues for the biological behavior of nanomaterials.

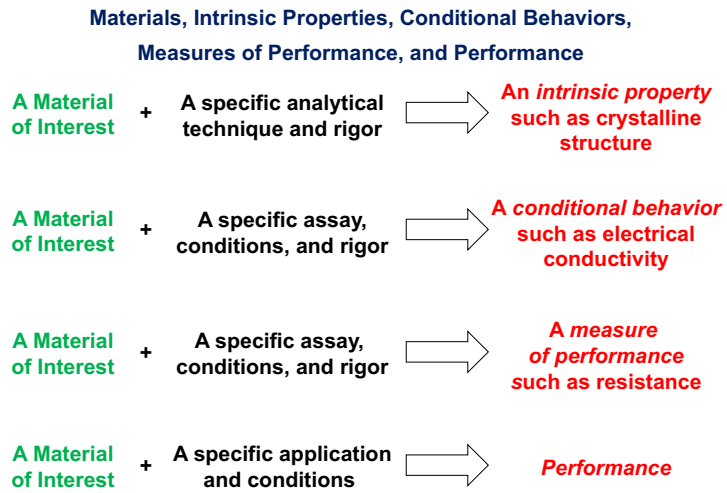


FIGURE 5.12

Intrinsic properties and conditional behavior issues related to the performance of nanomaterials and nanoenabled products.

concept for issues of the biological behavior of nanomaterials and for issues related to the performance of nanomaterials and nanoenabled products. Of special interest are any properties that have relevance to both health (implications) and performance (applications).

5.3.8 THE PARADOX OF IDEALIZED VERSUS REAL STUDY MATERIALS

Creating a relevant and reliable body of actionable and generalizable knowledge about the intrinsic properties and conditional behaviors of nanomaterials involves choosing which materials should be studied and using the findings of those studies to understand the behavior of other materials. A key question is "To what extent do measurements of idealized materials relate to the behaviors of real materials?" As illustrated in Fig. 5.13, the paradox of studying and understanding the myriad nanomaterials is that the increasingly "idealized" materials (those created under highly controlled conditions, with uniform characteristics, at high purity) are likely to be decreasingly "real" compared to what will practically be encountered in industry, medicine, or other applications; while the increasingly "real" materials are decreasingly "ideal" for use in studies to relate material characteristics to material behaviors (especially for mixtures and complex formulations, including those that change with age or handling conditions) (Hoover, 2008).

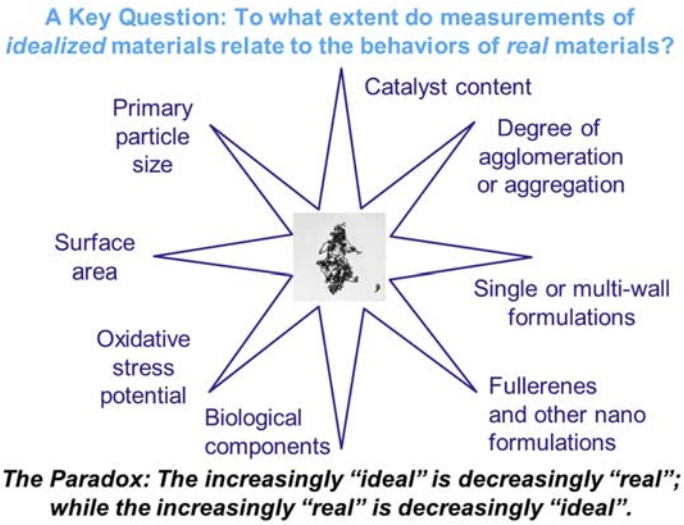


FIGURE 5.13

Illustration of Hoover's Paradox about the extent to which measurements of idealized study materials are able to inform our understanding of the behaviors of "real" materials that may be encountered in industry or other practice.

Adapted from Hoover, M.D., 2008. NanoMetrology Research at NIOSH, NIST – NIOSH Scientific Information Exchange, National Institute of Standards and Technology, Gaithersburg, MD, January 28, 2008.

5.4 PUTTING NANOINFORMATICS PRINCIPLES INTO PRACTICE

5.4.1 AN INFORMATION-TO-ACTION CONTINUUM

Fig. 5.14 presents an information-to-action continuum for enabling effective risk management for nanotechnology. The elements of the process have been used in the US–EU Communities of Research and build on a foundation of ontologies and databases. An exposure assessment element addresses potential exposures of ecosystems and humans that may occur during actual activities throughout the life cycle of a nanomaterial or a nanoenabled product. Based on realistic estimates of the routes and magnitudes of exposure, ecotoxicity testing and modeling can be conducted to assess environmental hazards, and mammalian toxicological studies can be performed to extrapolate risks to human health. Realistic combinations of exposure and hazard can then be evaluated to assess potential health-related risks. Realistic understanding of potential risks can then be used to design programs to effectively manage risks using approaches such as the hierarchy of control.

Fig. 5.15 describes a similar continuum for developing relevant and reliable ontologies and databases for nanomaterial properties, assessing incorporation of

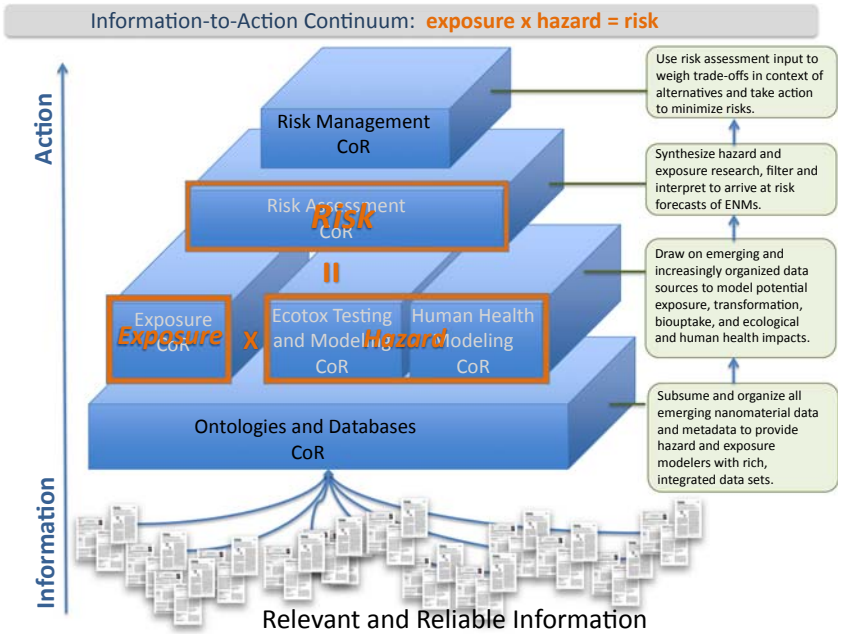


FIGURE 5.14

Information-to-action continuum for enabling effective risk management for nanotechnology.

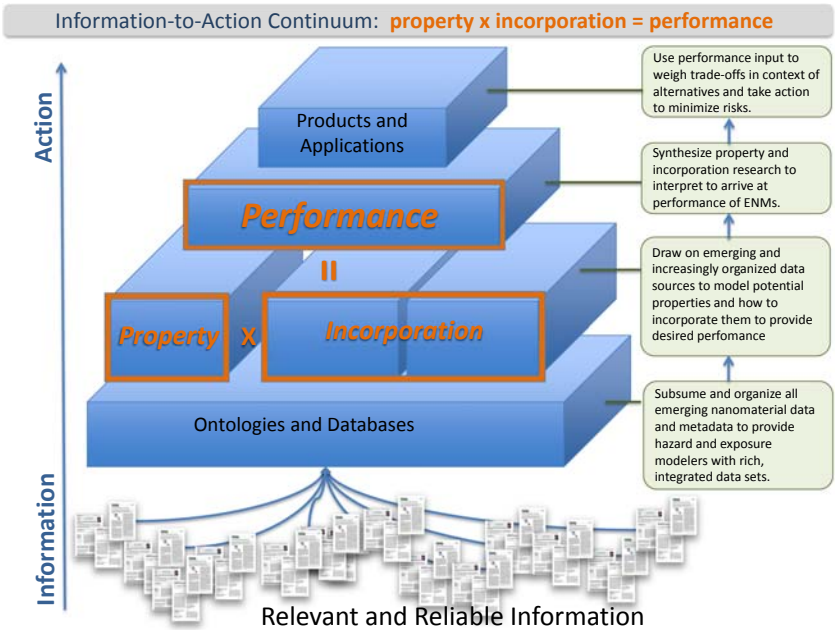


FIGURE 5.15

Information-to-action continuum for enabling effective development of nanoenabled products and applications.

those properties into materials and nanoenabled products, and assessing the resulting performance. Such information can enable effective development of products and applications.

5.4.2 A LIFE CYCLE APPROACH TO SAMPLING AND CHARACTERIZATION METHODS

Fig. 5.16 presents an overarching life cycle framework and decision-making process for the development, validation, selection and use of sampling and characterization methods. The life cycle concept was originally formulated as part of the consensus-standard process for use in emergency response situations (Hoover and Cox, 2004), adapted and applied for radioactive air sampling and instrumentation (Hoover and Cox, 2010), adopted as a systematic way to organize the framework of a US initiative on Nanotechnology for Sensors and Sensors for Nanotechnology (NNI, 2012), and most recently expanded to meet all manner of the emerging sensor needs for safety, health, well-being, and productivity (Hoover and Debord, 2015). Effective application of the life cycle process ensures that the sensor methods and instrumentation will work as intended under realistic conditions. Documentation and continuous improvement are essential at each step.

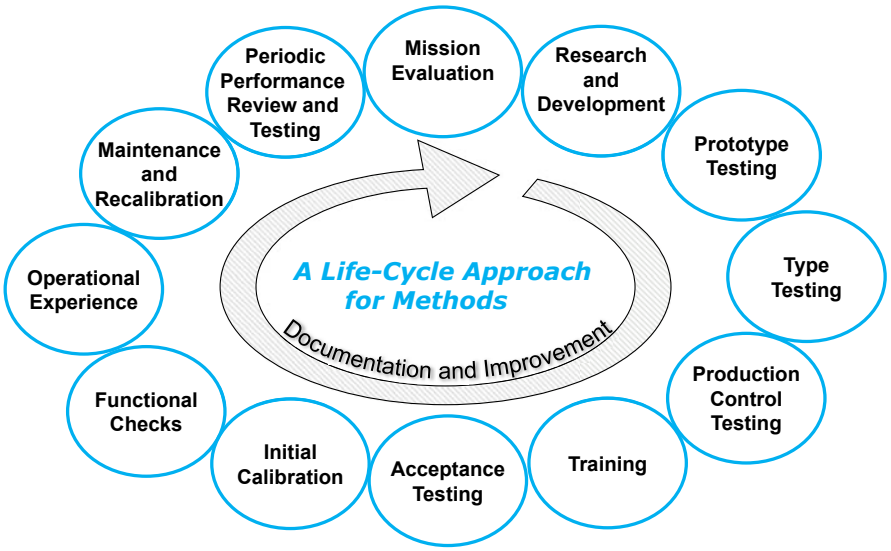


FIGURE 5.16

Life cycle approach for sampling and characterization methods. All steps are essential.
Adapted from Hoover, M.D., Cox, M., 2010. A life-cycle approach to development and application of air sampling methods and instrumentation. In: Maiello, M.L., Hoover, M.D. (Eds.), Radioactive Air Sampling Methods. CRC Press, Boco Raton, FL.

Mission evaluation. The life cycle begins with a clear identification of the purpose of the measurement, including what needs to be measured, under which conditions it needs to be measured, and how well it needs to be measured. Definition of the requirements for each of the steps in the comprehensive life cycle must be derived from an effective mission evaluation that includes identifying constraints on when, where, for what measurements, under what conditions, over what frequency and duration, and by whom the method or instrument is to be used. The evaluation and thorough understanding of mission objectives and the intended conditions of instrument use is the critical initial step of the instrument life cycle.

Research and development. Research and development is performed by the manufacturer or researcher to determine the likelihood that a specific instrument design or concept will meet the intended specifications. This includes balancing trade-offs of user requirements for limits of detection and response time against instrument size, weight, reliability, ease of use, cost, and training requirements. Development tests are normally conducted under "breadboard" conditions, in which subsystem performance is evaluated without a complete instrument configuration. Understanding the mission objectives, performance requirements, and expected conditions of use allows the manufacturer to develop an instrument that is likely to meet mission objectives and performance requirements.

Prototype testing. Prototype testing demonstrates that the design of an instrument is likely to meet certain specifications, including ease of use. Although prototype testing is not formally required by national or international standards, it is industrial practice that decreases the possibility that production units will fail to meet requirements of applicable standards. This testing phase also provides opportunities to ensure functionality under any special operational controls that may be required for specific situations and field applications (for example, provision of highly readable displays, audible alarms, and easy-to-operate dials for use with PPE that may restrict vision, hearing, or touch).

Type testing. Type testing is the first formal requirement of national and international standards. Some standards have been developed for nanomaterial characterization methods. To fully define the performance and limitations of an instrument, such standards require that the instrument be type tested in accordance with requirements detailed in the applicable standards. Type testing is typically performed on two or more production models of each instrument to fully characterize the performance of the instrument. The essential elements of instrument performance type testing (in the most desirable sequence) are detection response sensitivity and specificity, electrical/electronic, mechanical, and environmental. Instruments that fail at any point in the test sequence need not be additionally tested. The test sequence should be reinitiated if design modifications are made to correct the performance deficiency. In other words, the design of an instrument failing the radiological tests should be modified for improvement and retesting before electrical/electronic tests are initiated. The range of required tests addresses concerns that the accuracy of measurements during field use can be affected by variation in source or agent characteristics, instrument orientation with respect to the source, temperature, humidity, and instrument stability. Other tests, such as vibration and drop tests, address the ruggedness of the instrument. The instrument performance, as defined by results of the type test and the standard-specified interpretation of the test data, will document for the user how accurately the instrument can be expected to detect and quantify the nanomaterial chemical, biological, radiological agent of concern under a range of operational conditions.

Production control testing. Production control testing has not generally been a formal step in the standards process for individual classes of radiological (or chemical or biological) instrumentation. However, production quality management and quality assurance do fall under the manufacturer requirements delineated by the International Organization for Standardization (ISO) under the ISO 9000 standards (ISO, 2015a,b). Compliance with ISO 9000 includes a Plan-Do-Check-Act (PDCA) approach (ISO, 2008) that is similar to the life cycle approach described here. PDCA is sometimes referred to as Plan-Do-Check-Adjust to clarify that the fourth step in the PDCA cyclical process is to take action to adjust how the work is being done. The PCDA approach is also recommended in the American National Standard for Safety Management Systems (ANSI/ASSE, 2012). General attention to having and following a set of business procedures may not necessarily ensure that all critical factors for identifying and correcting instrument errors or defects are

addressed. Production control testing represents good practice to ensure that instruments meet critical requirements. Higher performance and reliability are especially important for homeland security applications. Production control testing is performed by the manufacturer in accordance with documented procedures. In some cases, purchasers make agreements with the manufacturer to ensure that specific requirements are met.

Training. Training is a crucial crosscutting step conducted at each phase of the life cycle. The central positioning of training in Fig. 5.16 indicates that it applies backward to instrument developers and forward to instrument users. Effective engagement from all life cycle participants and their associated training organizations about the realities of instrument requirements, use, and interpretation is essential to ensuring that training is relevant and reliable. The most notable training issues for practitioners apply to individuals who will operate the instrumentation and interpret and act on its results. If training needed to conduct any of the steps is inadequate, then the critical contributions of that step are likely to be inadequate.

Acceptance testing. Acceptance testing should be performed by the purchaser or user on each new instrument before initial use. Acceptance testing should test each instrument against specific characteristics identified as critical or indicative of overall instrument performance. The purpose of acceptance testing is to demonstrate that the specifications of the end-user, usually stated in a formal contractual agreement with the manufacturer, are met. An acceptance test generally consists of physical inspection, general operational tests, and appropriate response tests. Some aspects of acceptance testing, such as response testing, may be completed under type testing (above) as agreed on between the user and manufacturer. An example would be type testing a detection system that need only be done one time with a calibrated standard reference material specimen.

Initial calibration. The initial instrument calibration is frequently performed as part of the acceptance test. Initial calibration can also be performed at any time after general acceptance but before initial use of the instrument. However, some instruments are factory calibrated and do not require additional calibration. For other instruments (as noted in the type testing section above), the "initial" calibration is performed as part of the type test using the radionuclide of concern. When initial calibration has been established during type testing or at the factory, calibration checks or verifications by the purchaser or user may be appropriate. When surrogate solid photon sources and/or electroplated sources have been used simultaneously during the initial calibration, they can be used as secondary standard sources in subsequent calibrations. For instruments being held in reserve for future use, the initial calibration may be performed at a later date.

Functional checks. A preoperational functional check is a check, often qualitative, to determine that an instrument is operational and capable of performing its intended function. Functional checks are sometimes referred to as "operational checks" or "operability checks." Such checks may include, for example, battery check, zero setting, or source response check. Many modern instruments include automatic diagnostic and self-checking features. For radiation detection

instrumentation, functional checks may include response to natural background radiation. For biological or chemical detection instrumentation, checks may include response to ambient materials or may require the artificial introduction of test materials. All or a subset of these checks are typically performed at least daily, or prior to each intermittent use, whichever is less frequent. In many instances, functional checks must be documented to validate subsequently acquired data.

Operational experience. The intelligent observation and review of operational experience can provide early evidence of instrument performance deficiencies. For example, deviations of instrument results during temperature or humidity excursions may indicate that the instrument seals or sensors are damaged or that the instrument itself does not have adequate stability features. Unexpectedly, high readings in the presence of electric-arc welding operations may indicate that an instrument is susceptible to electromagnetic interference. The review and documentation of inconsistencies observed during operational experience is not necessarily a statutory or consensus-standard requirement, but it is recommended practice.

Maintenance and recalibration. Maintenance must be performed using components at least equivalent to those specified by the manufacturer. Replacement components must be manufacturer-specified or equivalent. Repairs made using unapproved instructions or components that may affect instrument performance constitute an instrument modification and must render invalid any type tests made on the instrument model as applied to the specific instrument. Modified instruments must have their performance tested and documented prior to issuance for field use. If the user can document that the modification does not affect the instrument performance, additional testing is not required. For example, modifying the size or shape of a control knob to enable its use with protective gloves might be a valid modification that would not require additional testing. However, if modifications deal with the instrumental operating principle, then additional testing would be required.

Recalibration of an instrument or system may be performed by the user or by a contracted and qualified facility at a frequency either required by applicable regulation, suggested by recommendations for good practice, indicated as necessary and sufficient by operating experience, or as allowed by a combination of the instrument design and the conditions of use. The frequency of maintenance and recalibration is typically set at 1 year, but if performance history indicates that the instrument is sufficiently reliable (e.g., recalibration as-found data is within tolerance $> 95\%$ of the time), less frequent recalibrations may be performed, provided the recalibration frequency does not exceed 3 years. An example motivation for less frequent recalibrations is if the monitor is not routinely accessible (i.e., during periods of nanomaterial production in an isolated system).

Periodic performance testing. Periodic performance testing is needed to determine if instruments continue to provide adequate performance under existing or altered conditions of use. Aging and degradation of critical instrument components are also a concern. Based on experience and anticipated modes of failure, the purchaser should test or arrange to test a representative number of units against selected specifications from the type test to verify that the instrument continues to

meet relevant specifications. Individual units, models, or families of instruments should be modified or removed from service when they no longer meet operational needs. The life cycle step of periodic performance testing should also be viewed as an opportune time to reevaluate mission needs and instrument options. It should also be viewed as an opportunity to adopt or develop improved tests or test-agent characteristics to better reflect instrument performance in the real world.

5.4.3 A GRADED APPROACH TO SAMPLING AND CHARACTERIZATION

As illustrated in Fig. 5.17 and detailed below, programs can use a graded approach to sampling and characterization involving

- Level 0 prioritization of sampling needs (Which processes should be characterized?)
- Level 1 initial screening and detection (What sampling and analytical methods are needed for initial screening and detection of a material of potential concern?)
- Level 2 comprehensive characterization and detection (What methods are needed for comprehensive characterization and assessment of the material so that its properties and control requirements are fully understood?)
- Level 3 routine monitoring and control (What subset of the screening and characterization methods is necessary and sufficient for routine monitoring and control of the material and situation of interest?)

Level 0	Level 1	Level 2	Level 3
Prioritization of Sampling Needs	**Intitial Screening and Detection**	**Comprehensive Characterization and Assessment**	**Routine Monitoring and Control**
• Process knowledge - Work flows - Anticipated or recognized hazards and potentials for exposure	• Process knowledge • Gross mass or activity counting • Optical particle counting • Condensation particle counting • Microscopy	• Composition - Elemental and chemical • Particle size - Physical, aerodynamic, thermodynamic, electrical mobility • Concentration - Peak, mean, variability • Biophysical factors - Shape, surface area, solubility • Other factors relevant to the assessment	• A necessary and sufficient subset of Level 1 and Level 2 methods for the material and situation of interest

FIGURE 5.17

Organization of a graded approach to sampling and characterization of nanomaterials.

Adapted from Hoover, M.D., 2010. Methods for Comprehensive Characterization of Radioactive Aerosols: A Graded Approach. In: Maiello, M.L., Hoover, M.D. (Eds.), Radioactive Air Sampling Methods. CRC Press, Boco Raton, FL.

The organization of a graded approach to sampling was described for use in sampling for airborne radioactivity (Hoover, 2010), recommended for use in sampling for nanomaterials (Kulinowski and Lippy, 2011a), and reflected in the nanomaterial exposure assessment technique (Eastlake et al., 2016). The significant cost and time factors associated with characterizing nanomaterials, especially aerosols of nanomaterials, make it especially important that all aspects of any measurements be soundly justified. Given the diverse options for sampling and characterization, decisions need to be made about when sampling is needed and which methods should be used.

Prioritization of sampling needs. This time and resource-saving Level 0 step ensures focus on areas of concern. Inputs include process knowledge, work flows, anticipated or recognized hazards, and potential for exposure.

Initial Screening and Detection. Sampling for initial screening and detection is performed to determine whether conditions of concern exist in a workplace or environmental situation. Typical components of a "Level 1" characterization include

- process knowledge as an indication of whether material of concern might be present and available for dispersion,
- gross mass or activity counting of air sampling results, and,
- when concentrations of inert background materials are low relative to concentrations of the aerosol of concern, optical particle counting or condensation particle counting to compare air concentrations before, during, and after process activities.

Samples collected by filtration or other methods are typically examined by electron microscopy or other microscopic techniques to assess the presence of materials of concern.

Comprehensive characterization and assessment. Comprehensive characterization and assessment is conducted when there is an indication that surface or airborne concentrations of hazardous materials at a level that requires additional information to evaluate the adequacy of controls or the potential consequences of exposure. As illustrated in Fig. 5.15, the techniques used for "Level 2" characterization and assessment can be targeted to reveal information about the nanomaterial aerosol's elemental composition, chemical composition, particle diameter (physical, aerodynamic, thermodynamic, or electrical mobility), particle morphology, surface area, biological solubility, and other relevant properties that would influence decisions about management of control or consequences.

The guiding principle is as follows: would information from application of a possible characterization method influence decisions regarding the need to control a material or steps that should be taken in the event that control is lost? Many studies have involved a suite of characterization methods.

Routine monitoring and control. The objective and challenge for routine monitoring and control is to select a necessary and sufficient subset of Level 1 and 2 methods for characterizing the material and situation of interest. If routine assessment of a parameter is not important for confirming or altering work practices or

workplace controls, then methods to assess that parameter are not needed as part of the "Level 3" effort.

Emphasis should be on selection of an economical and efficient set of measurements that will simultaneously confirm important aerosol properties and reveal any important changes in aerosol concentrations or characteristics that might require investigation or action. Investigation and response can include reintroduction of Level 2 characterization methods. For example, microscopic examination of particle morphology can reveal whether something in the chemistry, composition, or temperature history has changed. The appearance of irregular (rather than spherical) particles might indicate that process temperatures are lower than normal or that the residence time of an aerosol at elevated temperature is shorter than normal.

5.4.4 FOUR STEPS TO A TOTAL CULTURE OF SAFETY, HEALTH, WELL-BEING, AND PRODUCTIVITY

To build on individual efforts by readers, writers, reviewers, and practitioners, it makes sense to view clear communication as a community effort involving everyone who may be concerned about an issue or able to take action to create a favorable outcome for an issue. As illustrated in Fig. 5.18, fostering community understanding and application of the decision-making framework to build and sustain a total culture of safety, health, well-being, and productivity requires a community effort through the following four steps:

1. engage the community;
2. inform the interested;
3. reward the responsive; and
4. understand and incentivize the reluctant.

FIGURE 5.18

Four steps for community actionto achieve safety, health, well-being, and productivity.

From Hoover, M.D., Cash, L.J., Mathews, S.M., Feitshans, I.L., Iskander, J., Harper, S.L., 2014. 'Toxic' and 'nontoxic': confirming critical terminology concepts and context for clear communication. In: Wexler, P., (Ed.), Encyclopedia of Toxicology, vol. 4, third ed. Elsevier, Oxford, pp. 610–616.

5.5 FOSTERING CONSENSUS ON SOUND KNOWLEDGE MANAGEMENT AND INFORMATICS TOOLS

From the outset, nanotechnology has been a multidisciplinary field. In a simplistic sense, it extends materials science beyond compositional considerations and into phenomena such as quantum confinement, surface-dominated reaction chemistry, catalysis, and drug design. Each of these fields has its own traditions regarding terminology, chemical modeling, test protocols, data interpretation, and the like; as well as its own cultural aspects and cultural differences when placed in a global perspective. This is especially the case with medical uses, where the standard differentiation between a drug and a device is less obvious when working with nanoscale materials. Similarly, applying the concept of positive controls to materials with a particle/chemical duality is not a straightforward extension of traditional biological test protocols.

Because of the multidisciplinary challenges and opportunities of nanotechnology and nanoinformatics, we recognize the need to bridge areas, including biomedicine, nanotechnology regulation, environmental health and safety, occupational health and safety, computational nanotechnology and informatics, toxicology (eco and otherwise), industrial process design, patents and intellectual property, and legal requirements of nanotechnology.

The accompanying chapters of *Nanotechnology Environmental Health and Safety: Risk, Regulation, and Management* present examples of how safety issues in nanotechnology are currently being applied or envisioned to be applied in research and development programs, professional societies, standards bodies, and industries. Those examples illustrate what has been learned through experience to date and also include some of the difficulties in developing common understandings. Consistent with the purpose of this book, the presentations of real-life practices serve to educate and inform readers and support lifelong learning about the methods and applications of prudent safety practices approaches in nanotechnology and related fields. We can all work together to foster a growing national and international consensus on technically sound knowledge management and informatics tools that can support the rational design of nanomaterials and products, prioritization of research, and assessment of risk across the nanoenabled product life cycle.

ACKNOWLEDGMENTS

Many individuals have contributed to defining, developing, and advancing the science and practice of nanoinformatics. Many of them are noted in the list of references. They all deserve credit for their contributions. The authors gratefully acknowledge the support of their respective organizations. The findings and conclusions in this document are those of the authors and do not necessarily represent the views of their respective organizations.

REFERENCES

American Industrial Hygiene Association (AIHA), 2015a. The AIHA Nanotechnology Working Group, American Industrial Hygiene Association, Falls Church, VA. Available at: https://www.aiha.org/get-involved/VolunteerGroups/Pages/Nanotechnology-Working-Group.aspx.

American Industrial Hygiene Association (AIHA), 2015b. Personal Protective Equipment for Engineered Nanoparticles, Fact Sheet by the AIHA Nanotechnology Working Group, American Industrial Hygiene Association, Falls Church, VA. Available at: https://www.aiha.org/government-affairs/Documents/Personal%20Protective%20Equipment%20for%20Engineered%20Nanoparticles_Final.pdf.

American National Standards Institute/American Society of Safety Engineers (ANSI/ASSE), 2011. PtD Standard Z590.3.2011, Prevention through Design: Guidelines for Addressing Occupational Risks in Design and Redesign Processes. American National Standards Institute/American Society of Safety Engineers, Des Plains, IL.

American National Standards Institute/American Society of Safety Engineers (ANSI/ASSE), 2012. Z10. Safety Management Systems. American National Standards Institute/American Society of Safety Engineers, Des Plains, IL.

Barrie, M.D., Baker, J., Hoover, M.D., Geraci, C.L., 2017. Nanobiomonitoring and surveillance: opportunities to confirm the protection of nanomaterial workers. The Synergist 28 (2), 28–31.

Baker, N.A., Klemm, J.D., Harper, S.L., Gaheen, S., Heiskanen, M., Rocca-Serra, P., Sansone, S.A., 2013. Standardizing data. Nature Nanotechnology 8, 73–74.

Brandt, M.T., 2010. Industrial hygiene in the 21st century. The Synergist 21 (8), 8.

de la Iglesia, D., Harper, S., Hoover, M.D., Klaessig, F., Lippell, P., Maddux, B., Morse, J., Nel, A., Rajan, K., Reznik-Zellen, R., Tuominen, M.T., 2011. Nanoinformatics 2020 Roadmap. National Nanomanufacturing Network. University of Massachusetts Amherst, Amherst, MA. Available at: http://eprints.internano.org/607/.

Eastlake, A., Beaucham, C., Martinez, K., Dahm, M., Sparks, C., Hodson, L., Geraci, C., 2016. Refinement of the nanoparticle emission assessment technique into the nanomaterial exposure assessment technique (NEAT 2.0). Journal of Occupational and Environmental Hygiene 13 (9), 708–717.

Erdely, A., Dahm, M.M., Schubauer-Berigan, M.K., Chen, B.T., Antonini, J.M., Hoover, M.D., 2016. Bridging the gap between exposure assessment and inhalation toxicology: some insights from the carbon nanotube experience. Journal of Aerosol Science 99, 157–162.

Feitshans, I.L., 2013. Designing an Effective OSHA Compliance Program, Sections Concerning Corporate Compliance Programs for Nanotechnology Industries. Thomson Reuters Westlaw, Eagan, MN.

Feitshans, I.L., 2018. Global Health Impacts of Nanotechnology Law. Pan Stanford Publications, Singapore.

Franklin, C., Kader, G., Mewborn, D., Moreno, J., Peck, R., Perry, M., Scheaffer, R., 2007. Guidelines for Assessment and Instruction in Statistics Education (GAISE) Report. American Statistical Association, Alexandria, VA. Available at: http://www.amstat.org/education/gaise/.

Harper, S.L., Hutchison, J., Baker, N., Ostraat, M., Tinkle, S., Steevens, J., Hoover, M.D., Adamick, J., Rajan, K., Gaheen, S., Cohen, Y., Nel, A., Cachau, R., Tuominen, M., 2013. Nanoinformatics infrastructure: current resources, community needs, and the

proposal of a collaborative framework for data sharing and information integration. Computational Science & Discovery 6, 1–13.
Hendren, C.O., Powers, C.M., Hoover, M.D., Harper, S.L., 2015. The nanomaterial data curation initiative: a collaborative approach to assessing, evaluating, and advancing the state of the field. Beilstein Journal of Nanotechnology 6, 1752–1762.
Hoover, M.D., January 28, 2008. NanoMetrology Research at NIOSH, NIST – NIOSH Scientific Information Exchange. National Institute of Standards and Technology, Gaithersburg, MD.
Hoover, M.D., 2010. Methods for Comprehensive Characterization of Radioactive Aerosols: A Graded Approach. In: Maiello, M.L., Hoover, M.D. (Eds.), Radioactive Air Sampling Methods. CRC Press, Boco Raton, FL.
Hoover, M.D., Cox, M., 2004. A life-cycle approach for development and use of emergency response and health protection instrumentation. In: Brodsky, A., Johnson, R.H., Groans, R.E. (Eds.), Public Protection from Nuclear, Chemical, and Biological Terrorism: Health Physics Society 2004 Summer School. Medical Physics, Madison, WI.
Hoover, M.D., Cox, M., 2010. A life-cycle approach to development and application of air sampling methods and instrumentation. In: Maiello, M.L., Hoover, M.D. (Eds.), Radioactive Air Sampling Methods. CRC Press, Boco Raton, FL.
Hoover, M.D., Debord, D.G., 2015. Turning numbers into knowledge: sensors for safety, health, well-being, and productivity. Synergist 26, 22–26.
Hoover, M.D., Rickabaugh, K.P., 2014. Quality assurance considerations for nanoparticles. In: Eide, M. (Ed.), AIHA Laboratory Quality Assurance Manual. American Industrial Hygiene Association, Falls Church, VA, pp. 121–132.
Hoover, M.D., Armstrong, T., Blodgett, T., Fleeger, A.K., Logan, P.W., McArthur, B., Middendorf, P.J., 2011. Confirming our industrial hygiene decision-making framework. The Synergist 22 (1), 10.
Hoover, M.D., Cash, L.J., Mathews, S.M., Feitshans, I.L., Iskander, J., Harper, S.L., 2014. 'Toxic' and 'nontoxic': confirming critical terminology concepts and context for clear communication. In: Wexler, P. (Ed.), Encyclopedia of Toxicology, third ed., vol. 4. Elsevier, Oxford, pp. 610–616.
Hoover, M.D., Myers, D.S., Cash, L.J., Guilmette, R.A., Kreyling, W.G., Oberdörster, G., Smith, R., Cassata, J.R., Boecker, B.B., Grissom, M.P., 2015. Application of an informatics-based decision-making framework and process to the assessment of radiation safety in nanotechnology. Health Physics 108 (2), 179–194.
International Organization for Standardization, 2008. ISO 9000 Introduction and Support Package: Guidance on the Concept and Use of the Process Approach for Management Systems. ISO/TC 176/SC 2/N 544R3, Geneva, Switzerland. Available at: https://www.iso.org/files/live/sites/isoorg/files/archive/pdf/en/04_concept_and_use_of_the_process_approach_for_management_systems.pdf.
International Organization for Standardization, 2015a. Quality Management Systems - Fundamentals and Vocabulary. ISO 9000, Geneva, Switzerland.
International Organization for Standardization, 2015b. Systems and Software Engineering–System Life Cycle Processes. ISO/IEC/IEEE 15288:2015, Geneva, Switzerland.
Iskander, J.K., 2012. Scientific Reviewing for Physicians: A CLEAR Approach. Public Health Service Medical Category. Centers for Disease Control and Prevention, Atlanta, GA.
Iskander, J.K., Calugar, A., Peavy, R.D., Sowell, A., 2017. Scientific document review at the centers for disease control and prevention: the CLEAR approach. American Journal of Public Health 107 (6), 858–859.

Jahn, S.D., Bullock, W.H., Ignacio, J.S. (Eds.), 2015. A Strategy for Assessing and Managing Occupational Exposures. American Industrial Hygiene Association, Falls Church, VA.

Karcher, S., Willighagen, E.L., Rumble, J., Ehrhart, F., Evelo, C.T., Fritts, M., Gaheen, S., Harper, S.L., Hoover, M.D., Jeliazkova, N., Lewinski, N., Marchese Robinson, R.L., Mills, K.C., Mustad, A.P., Thomas, D.G., Tsiliki, G., Hendren, C.O., 2018. Integration among databases and data sets to support productive nanotechnology: challenges and recommendations. NanoImpact 9, 85−101.

Kulinowski, K., Lippy, B., 2011a. Engineered nanoparticles. In: Anna, D.H. (Ed.), The Occupational Environment: Its Evaluation, Control, and Management, third ed., vol. 1. American Industrial Hygiene Association, Falls Church, VA, pp. 629−662.

Laszcz-Davis, C.A., Maier, A., Perkins, J., 2014. The Hierarchy of OELs: a new organizing principle for occupational risk assessment. The Synergist 25 (3), 27−30.

Marchese Robinson, R.L., Lynch, I., Peijnenburg, W., Fritts, M., Rumble, J., Klaessig, F., Hendren, C.O., Marquardt, C., Rauscher, H., Puzyn, T., Purian, R., Åberg, C., Karcher, S., Gaheen, S., Vriens, H., Hoet, P., Hoover, M.D., Ku, S., Harper, S., 2016. How should the completeness and quality of curated nanomaterial data be evaluated? Nanoscale 8, 9919−9943.

National Academy of Sciences/National Research Council, 1983. Risk Assessment in the Federal Government: Managing the Process. National Academy Press, Washington, DC.

National Academies/National Research Council, 2009. Science and Decisions: Advancing Risk Assessment. National Academies Press, Washington, DC.

National Council on Radiation Protection and Measurements (NCRP), 2017. Radiation Safety Aspects of Nanotechnology. NCRP Report No. 176. National Council on Radiation Protection and Measurements, Bethesda, MD.

National Institute for Occupational Safety and Health (NIOSH), 2009. Approaches to Safe Nanotechnology: Managing the Health and Safety Concerns Associated with Engineered Nanomaterials. DHHS (NIOSH) Publication No. 2009-125. NIOSH, Cincinnati, OH. Available at: https://www.cdc.gov/niosh/docs/2009-125/pdfs/2009-125.pdf.

National Institute for Occupational Safety and Health (NIOSH), 2011. Occupational Exposure to Titanium Dioxide. DHHS (NIOSH) Publication No. 2011-160. NIOSH, Cincinnati, OH. Available at: https://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf.

National Institute for Occupational Safety and Health (NIOSH), 2013. Occupational Exposure to Carbon Nanotubes and Nanofibers. DHHS (NIOSH) Publication No. 2013-145. NIOSH, Cincinnati, OH. Available at: https://www.cdc.gov/niosh/docs/2013-145/pdfs/2013-145.pdf.

National Institute for Occupational Safety and Health (NIOSH), 2018a. Workplace Design Solutions: Protecting Workers during Nanomaterial Reactor Operations. DHHS (NIOSH) Publication No. 2018-120. NIOSH, Cincinnati, OH. Available at: https://www.cdc.gov/niosh/docs/2018-120/default.html.

National Institute for Occupational Safety and Health (NIOSH), 2018b. Workplace Design Solutions: Protecting Workers during the Handling of Nanomaterials. DHHS (NIOSH) Publication No. 2018-121. NIOSH, Cincinnati, OH. Available at: https://www.cdc.gov/niosh/docs/2018-121/default.html.

National Institute for Occupational Safety and Health (NIOSH), 2018c. Workplace Design Solutions: Protecting Workers during Intermediate and Downstream Processing of Nanomaterials. DHHS (NIOSH) Publication No. 2018-120. NIOSH, Cincinnati, OH. Available at: https://www.cdc.gov/niosh/docs/2018-122/default.html.

National Nanotechnology Initiative (NNI), July 2012. Nanotechnology Signature Initiative White Paper: Nanotechnology for Sensing and Sensing for Nanotechnology: Improving Safety, Health, and the Environment, National Science and Technology Council, Committee on Technology, Subcommittee on Nanoscale Science, Engineering, and Technology. U.S. National Nanotechnology Initiative, White House Office of Science and Technology Policy, Washington, DC. Available at: www.nano.gov/node/847.

National Nanotechnology Initiative (NNI), 2013. Nanotechnology Signature Initiative: Nanotechnology Knowledge Infrastructure (NKI) Data Readiness Levels Discussion Draft, National Science and Technology Council, Committee on Technology, Subcommittee on Nanoscale Science, Engineering, and Technology. U.S. National Nanotechnology Initiative, White House Office of Science and Technology Policy, Washington, DC. Available at: www.nano.gov/node/1015.

Powers, C.M., Mills, K.A., Morris, S.A., Klaessig, F., Gaheen, S., Lewinski, N., Ogilvie Hendren, C., 2015. Nanocuration workflows: establishing best practices for identifying, inputting, and sharing data to inform decisions on nanomaterials. Beilstein Journal of Nanotechnology 6, 1860−1871.

Schulte, P.A., Geraci, C.L., Murashov, V., Kuempel, E.D., Zumwalde, R.D., Castranova, V., Hoover, M.D., Hodson, L., Martinez, K.F., 2014. Occupational safety and health criteria for responsible development of nanotechnology. Journal of Nanoparticle Research 16 (1), 2153.

Schulte, P.A., Roth, G., Hodson, L.L., Murashov, V., Hoover, M.D., Zumwalde, R., Kuempel, E.D., Geraci, C.L., Stefaniak, A., Castranova, V., Howard, J., 2016. Taking stock of the occupational safety and health challenges of nanotechnology: 2000-2015. Environmental Health Perspectives 18, 159.

Thomas, D.G., Klaessig, F., Harper, S.L., Fritts, M., Hoover, M.D., Gaheen, S., Stokes, T.H., Reznic-Zellen, R., Freund, E.T., Klemm, J.D., Paik, D.S., Baker, N.A., 2011. Informatics and standards for nanomedicine technology. Wiley Interdisciplinary Reviews: WIREs Nanomedicine and Nanobiotechnology 3, 511−532.

Wexler, P. (Ed.), 2014. Encyclopedia of Toxicology. Elsevier, New York.

Zebroski, E.L., 1991. Lessons learned from man-made catastrophes. In: Knief, R.A., Briant, V.B., Lee, R.B., Long, R.L., Mahn, J.A. (Eds.), Risk Management: Expanding Horizons in Nuclear Power and Other Industries. Hemisphere Publishing, New York, pp. 51−65.

Zimmerman, J.B., Anastas, P.T., 2015. Toward substitution with no regrets. Science 347 (6227), 1198−1199.

FURTHER READING

Hoover, M.D., Stefaniak, A.B., Day, G.A., Geraci, C.L., 2007. Exposure assessment considerations for nanoparticles in the workplace. In: Monteiro-Riviere, N.A., Tran, C.L. (Eds.), Nanotoxicology: Characterization, Dosing, and Health Effects. Informa Healthcare, New York, pp. 71−83.

Kulinowski, K., Lippy, B., 2011b. Training Workers on Risks of Nanotechnology. National Institute of Environmental Health Sciences. Available at: https://tools.niehs.nih.gov/wetp/index.cfm?id=537.