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# Redressing the Silent Interim: Precautionary Action & Short Term Tests in Toxicological Risk Assessment\*

Timothy Riley\*\*

## Introduction

In 1990, the National Research Council (NRC), under the authority of a United States congressional commission, began investigating the methods that the Environmental Protection Agency (EPA) uses to estimate toxicological risk. In its executive summary, the NRC concluded that “because of limitations on time, resources, scientific knowledge, and available data, EPA should generally retain its conservative, default-based approach to risk assessment for screening analysis in standard setting; however, several corrective actions are needed to make this approach more effective.”<sup>1</sup>

The two corrective areas the NRC recommends for incorporation into EPA’s traditional, default-based quantitative risk assessment methodology are: (1) development of an iterative approach to risk assessment, and (2) when reporting estimates of risk to decision-makers and the public, it should present not just point estimates, but also sources and magnitudes of uncertainty associated with such estimates. In 1996, the NRC also stated the importance of understanding risk characterization as both an analytical and participant-driven deliberative process, which ought to be problem-driven, accountable to the role of

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1 Committee on Risk Assessment of Hazardous Air Pollutants, National Research Council, *Science and Judgment in Risk Assessment* 14 (1994).

uncertainty in risk management and broadly inclusive of potential interest-holders.<sup>2</sup>

In this paper, I argue for incorporating “non-traditional” precautionary measures with the procedural recommendations of the NRC into traditional toxicological risk assessment practices. Such inclusion of a precautionary disposition is most critical during the interim period of a toxicological risk assessment. Particularly in a post-market regulatory situation, a potential toxicological hazard may have been present in the environment and exposing human and animal populations for a period of time, perhaps even years, before the hazard was identified. Often, assessment of the potential danger and corrective action, if necessary, must be initiated quickly after identification.

This raises an important technical, political, and ethical question: Once a potential toxicological hazard has been identified, what actions ought to be taken to ensure public health and ecological integrity? Adherents of traditional toxicological risk assessment and advocates of the Precautionary Principle both offer competing paradigms about how to answer this question. In an attempt to combine elements from each paradigm, I will address this question by focusing on the NRC’s first corrective area — the development of an iterative approach methodology and discussion of the importance of using Short-Term Tests (STTs) as precautionary indicators of possible toxicological danger associated with potentially carcinogenic substances during the interim phase of toxicological risk assessments.

An iterative approach to risk assessment supports the idea of initially using less expensive and time consuming testing procedures that can quickly isolate potentially harmful persistent toxic chemicals from potentially harmless ones. The use of short-term tests, which are specific testing procedures designed for inexpensive preliminary screening, would streamline EPA and state regulatory action. In this manner, STTs allow for sufficient resources to be used on a broader array of possible potentially toxic substances by minimizing testing costs and time and therein protecting the underlying normative assumption in any toxicological risk assessment — minimizing the social costs in reference to the potential risks of endangered public health and

<sup>2</sup> Committee on Risk Characterization, National Research Council, *Understanding Risk: Informing Decisions in a Democratic Society* 2-5 & 164-165 (1996).

ecological integrity.

### A Backlogged and Failing Regulatory System

Regarding the concerns of toxic emissions and carcinogen risk, in 1987, the Congressional Office of Technology Assessment reported that federal regulatory standards had only identified a minority of potential carcinogens.<sup>3</sup> Over 80,000 chemicals were estimated to be in use in the United States, with over 2,000 new ones introduced annually.<sup>4</sup> Although few of these chemicals are likely to pose a significant human or environmental health risk, we nevertheless know little or nothing about their potential carcinogenic properties, in part because of the time and expense of conducting toxicological risk assessments. This sluggish pace of identification and, consequently, regulation under current toxic control policies has stirred public demand for reform of America's environmental management, of toxics, as the current regulatory process is marred by the immense amount of interim time necessary to complete a toxicological risk assessment.<sup>5</sup> Conceptualized as a necessary component for environmental decision-making, toxicological risk assessment, through measurement, testing, and mathematical or statistical models seeks to balance the degree of risk permitted against the cost of risk reduction and other competing factors.<sup>6</sup>

The EPA toxicological risk assessment framework, which is conceptually similar to the NRC framework for human health risk assessments,<sup>7</sup> is divided into three phases: (1) problem formulation;

<sup>3</sup> Congressional Office of Technology Assessment, OTA-BP-H-42, *Identifying and Regulating Carcinogens* (1987).

<sup>4</sup> Congressional Office of Technology Assessment, OTA-BP-ENV-166, *U.S. Congress Screening and Testing Chemicals in Commerce*, Washington: Office of Technology Assessment 126 (1995).

<sup>5</sup> See David Roe, *An Incentive Conscious Approach to Toxic Chemical Control*, 3 *Econ. Dev. Q.* 179 (1989).

<sup>6</sup> See Christoph Remann-Sutter, *Involving Others: Towards an Ethical Concept of Risk*, 9 *Risk: Health, Safety & Environment* 119 (1998) (critiquing this construction of risk assessment); cf. Kristin Shrader-Frechette, *Scientific Method, Anti-Foundationalism and Public Decisionmaking*, 1 *Risk: Health & Safety* 23 (1990); Kristin Shrader-Frechette, *How Some Risk Frameworks Disenfranchise the Public*, 8 *Risk: Health, Safety & Environment* 1 (1997); Kristin Shrader-Frechette, *Perceived Risks Versus Actual Risks: Managing Hazards Through Negotiation*, 1 *Risk: Health & Safety* 341 (1990).

<sup>7</sup> Risk Assessment Forum, Environmental Protection Agency, EPA/630/R-92/001, *Framework for Ecological Risk Assessment* 3 (1992).

(2) analysis; and (3) risk characterization. The interim can be considered the “analysis phase” consisting of two activities — characterization of exposure and characterization of ecological effects. Once the preliminary characterization of exposure and effects are completed, as well as examination of scientific data and data needs, policy and regulatory issues, and site-specific factors to define the feasibility, scope, and objectives for the toxicological assessment, the time consuming process of collecting and analyzing the data begins.

As early as 1984, this regulatory system was failing. The National Academy of Sciences (NAS) reported a significant lack of data on health effects of most industrial chemical products. The NAS found that 78% of chemicals in high-volume commercial use lacked “minimal” toxicity testing. The Environmental Defense Fund in 1997 and EPA in 1998 noted that the situation was not improving. For the 3,000 high-production-volume chemicals (those with over one million pounds in commerce), the studies concluded that: 93% lack some basic chemical screening data; 43% have no basic toxicity data; and 51% of chemicals on the Toxic Release Inventory lack basic toxicity information (a large percentage of available information is based only on acute toxicity).<sup>8</sup> Also, the congressional Office of Technology Assessment acknowledged that federal regulatory agencies had insufficiently analyzed fewer than a third of the known carcinogens under each of their statutory mandates. Furthermore, the National Toxicology Program lists 144 known carcinogens testing positive in one or more animal bioassays, and 62 substances found positive in three or four animal studies, yet approximately only 15% of each group had been assessed by the EPA’s Carcinogen Assessment Group by 1987.<sup>9</sup>

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<sup>8</sup> Joel Tickner & Carolyn Raffensperger, *The Precautionary Principle in Action: A Handbook* 12 <<http://www.sehn.org/rtfdocs/handbook-rtf.rtf>> (accessed Feb. 2000). This handbook was written for the Science and Environmental Health Network.

<sup>9</sup> Carl F. Cranor, *The Normative Nature of Risk Assessment: Features and Possibilities*, 8 *Risk: Health, Safety & Environment* 123 (1997) (citing Congressional Office of Technology Assessment, *Identifying and Regulating Carcinogens 1* (1987)).

### Limitations of Traditional Toxicological Risk Assessment

Rarely, if ever, during the collection and analysis of data is precautionary action taken. Traditionally, risk management follows risk assessment, and never the two shall meet. Nevertheless, a key normative aspect of toxicological risk assessment is that it is extremely difficult or impossible to separate risk assessment from risk management.<sup>10</sup>

To a certain extent, a degree of separation between assessment and management is necessary and desirable because it encourages both assessors and managers to make explicit, epistemic warrants for their claims and thus make their conclusions and recommendations more objective.<sup>11</sup> Yet taken too far, such a paradigm creates a vacuum of accountability in part because many risk assessors ignore value assumptions in their methodological judgments, leading to uninformed and therefore faulty risk-management decisions.<sup>12</sup>

Yet, the notorious Red Book,<sup>13</sup> produced by the NRC Committee on the Institutional Means for Assessment of Risks to Public Health, presents a conceptual model of risk assessment as an objective scientific activity, distinct from risk management in its exclusion of ethical, political, and institutional values. The Red Book states: "If risk management considerations ... are seen to affect ... a risk assessment, the credibility of the assessment ... can be compromised."<sup>14</sup> The transition from data acquisition and analysis to policy implementations can be exceedingly long because of the want to stave off action until "decisive" confirmation of toxicological harm can be positively ascertained. Considerable time is usually required in order for scientists and risk assessors to generate "scientifically valid" data that can be properly analyzed with minimum risk of inaccuracies. As with the Toxic Substances Control Act (TSCA), this "good science" aspect of

<sup>10</sup> Committee on the Institutional Means for Assessment of Risks to Public Health, National Research Council, *Risk Assessment in the Federal Government: Managing the Process* 76 (1983)(hereinafter "Redbook").

<sup>11</sup> Kristin Shrader-Frechette, *Risk and Rationality* 43-44 (U. of Cal. Press 1991).

<sup>12</sup> Kristin Shrader-Frechette, *Evaluating the Expertise of Experts*, 6 *Risk: Health, Safety & Environment* 115, 116 (citing Ellen Silbergeld, *Risk Assessment and Risk Management: An Uneasy Divorce*, in *Acceptable Evidence: Science and Values in Risk Management* 107 (Deborah G. Mayo & Rachelle D. Hollander eds., 1991); Richard M. Sedman & Paul W. Hadley, Comment, *Risk Assessment and Risk Management: Mending the Schism*, 3 *Risk: Health & Safety* 189 (1992)).

<sup>13</sup> See *supra* n. 10.

<sup>14</sup> Redbook, *supra* n. 10, at 152.

toxicological risk assessment, without considering the normative social costs of its methodological paradigm, has left the world literally flooded with thousands of potentially toxic substances, many of which society is not even aware of because the screening system is so backlogged and inefficient.

The presumption that risk assessment can be free of normative assumptions is now a debunked *modus operandi*.<sup>15</sup> Social costs are intricately bound to the procedural and scientific costs associated with conducting toxicological risk assessments, and thus, normative presuppositions must be considered in articulating methodological data endpoints, as well as policy implications derived from those endpoints. Furthermore, the last three decades have seen much progress in exploring and revealing the interconnections between ecosystem integrity, public health, and economic development. Using risk analysis as one mechanism for determining the “certainty” of a potential toxicological hazard requires more than merely a quantitative analysis. Also required is an understanding of the concepts of equity and fairness, the nature of cumulative risk, redefined notions of time frames for the persistence of chemicals, and an appreciation for market mechanisms such as incentives, cost-benefit analysis, and voluntary initiatives.<sup>16</sup>

Toxicological risk assessments are intrinsically pervaded with uncertainties, some of which can be accounted for and quantified, although others are pervasively indefinable (at least in a predictive schema).<sup>17</sup> Quantification and qualification of “risk” entails incorporating uncertainty as an operative component of our limited ability to understand causal pathways of toxicological fates, especially at the intersection of ecological integrity and public health. Absent perfect procedures, the alternative is to use processes that minimize resulting mistakes.

Carl Cranor argues that because of the prohibitive time and financial costs of properly conducting a toxicological risk assessment,

<sup>15</sup> William Ruckelshaus, *Risk, Science and Democracy*, 1 *Issues in Sci. and Tech.* 19 (1985).

<sup>16</sup> Michael D. Mehta, *Risk Assessment and Sustainable Development: Towards a Concept of Sustainable Risk*, 8 *Risk: Health, Safety & Environment* 137, 154 (1997).

<sup>17</sup> Tickner & Raffensperger, *supra* n. 8, at 11.

there is a normative imperative to seek out alternative methodologies that reduce overall costs and time.<sup>18</sup> This suggests the existence of an imperative to locate the minimum kind and amount of evidence necessary to judge the toxicity of substances to serve relevant social goals.

There can be significant social costs from slow risk assessments when environmental assessors and managers operate under the traditional risk assessment paradigm. On one hand, regulatory action initiated after a potentially toxic or carcinogenic chemical is released risks unnecessary toxic exposure until the chemical's toxicity is discovered and regulated. On the other hand, the costs from slow procedures themselves and opportunity costs resulting from the slow rate of assessment may leave unevaluated other toxic substances in commerce that could inflict serious injuries to public health and the environment. Inaction, too, can be costly. The inherent slowness of risk assessments, coupled with regulatory inertia, can keep possible life-saving and/or ecologically benign substances from reaching marketplaces.<sup>19</sup>

### Limitations of the Precautionary Principle

Precautionary Principle<sup>20</sup> adherents are concerned that risk assessments provide a false sense of security manifested in a milieu of quantitative, technical sophistication, while masking the inexact, assumption-laden, and at times, politically and economically driven science. Also, the burden-of-proof structure constituting the standards for scientifically rigorous conclusions facilitates a continuation of possibly greater pollution and degradation of public health under the premise that it is either safe or presents an acceptable risk. Critics of such a conceptual model argue that the separation of risk assessment and risk management, although superficially appealing, is an inadequate model for resolving complex social, political, and scientific problems that are uniquely bound in the problem formulation and risk characterization of a potentially carcinogenic substance. Citing several

<sup>18</sup> See Cranor, *supra* n. 9.

<sup>19</sup> *Id.*

<sup>20</sup> See *Protecting Public Health and the Environment: Implementing the Precautionary Principle* (Carolyn Raffensperger & Joel Tickner eds., 1999). This is an outstanding account of the Precautionary Principle.



previous works, Brown and Goble note that some argue that it would make “the field too sterile and routine and stifle the creative impulses of its practitioners, that it would result in addressing the wrong societal problems and thus be irrelevant, and it would be inappropriate on technical grounds.”<sup>21</sup> Advocates of the Precautionary Principle desire the explicit reincorporation of normative assumptions into the environmental regulatory schema.

The Precautionary Principle originates from Germany as the Vorsorgeprinzip, or “principle of foresight.” A fundamental aspect of the Precautionary Principle is that precautionary action ought to be taken before scientific certainty of cause and effect can be ascertained.<sup>22</sup> In recent years, the Precautionary Principle has figured prominently and contentiously in many international statements of policy, conventions, and national policies for sustainable development and environmental protection. At the heart of the debate lies one of the early tenants of the principle — the belief that society should in all its endeavors avoid environmental damage by careful forward-thinking planning and the elimination of dangerous levels of toxic chemicals.<sup>23</sup>

Although this is not a new idea, during the interim phase of a risk assessment, it is a rarity. In fact, even advocates of the Precautionary Principle are primarily interested in imposing preventive action at the “design stage of a potentially hazardous activity to ensure their greatest impact.”<sup>24</sup> Some precautionary actions that can be initiated during the

<sup>21</sup> Halina Szejnwald Brown & Robert L. Goble, *The Role of Scientists in Risk Assessment*, 1 *Risk: Health & Safety* 283, 285 (1990) (citing Dale Hattis & David Kennedy, *Assessing Risks for Health Hazards: An Imperfect Science*, 3 *Tech. Rev.* 60 (1986); Von Winterfelt, *Four Theses on the Application of Risk Assessment in Relation to Environmental Mutagens and Carcinogens*, in *Risk and Reason: Risk Assessment in Relation to Environmental Mutagens and Carcinogens* (P. Oftedal & A. Brogger, eds. 1986); Richard Wilson & W. Clark, *Risk Assessment and Risk Management: Separation Does Not Mean a Divorce*, in *Proceedings of the 1988 Annual Meeting of the Society for Risk Analysis*).

<sup>22</sup> The January 1998 Wingspread Statement on the Precautionary Principle states: “When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause-and-effect relationships are not fully established scientifically.” See Tickner & Raffensperger, *supra* n. 8, at 1.

<sup>23</sup> When speaking of acceptable levels of potentially dangerous toxicological hazards, Precautionary Principle advocates are interested primarily in the cumulative and synergistic effects on ecological systems. This often translates into significantly more stringent standards than, say, conducting a traditional quantitative risk assessment addressing only acute or chronic effects of substance.

<sup>24</sup> See Tickner & Raffensperger, *supra* n. 8.

interim period include bans and phase-outs, alternatives assessment, extremely conservative health-based occupational exposure limits, prima facie reverse onus chemical listing, and ecosystem management policies that ensure reversibility and flexibility.

These actions are designed to function immediately and for the most part, autonomously, from the need for scientific certainty. In fact, the onus of responsibility is placed on uncertainty as the operative phenomenon in which to gauge our assumptions of toxicological hazards. Such actions are almost exclusively focused on public health and rarely take into consideration economic and political stressors. Ozonoff articulates the concern of using only a precautionary approach for screening potential risks because such an approach, although increasing our sensitivity to predicting such threats, inadvertently takes an overly cautious stand when it is unnecessary.<sup>25</sup> Such an attitude is resource intensive and time-consuming, thus in many fundamental ways negating the primary purpose of a precautionary approach. Even precautionary action advocates who are willing to accept the incorporation of uncertainty (albeit quantified) into toxicological risk assessments through the use of model sensitivity analyses (e.g., Monte Carlo Simulations) are still faced with the daunting time consuming needs of collecting large enough databases for calculations. And as with any mathematical model, the results are only as good as the assumptions, and the choice of assumptions, particularly simplifying ones, is not always possible or heavily relies on the professional judgment (normative biases) of the assessor. The greater complexity also presents a significant challenge to effectively incorporating the public in the decisionmaking matrix during the interim phase (a key normative consideration for the Precautionary Principle).<sup>26</sup>

For the most part, bans and other immediate actions are politically dangerous and unacceptable in either a postmarket or premarket setting where economic and social investment issues are of critical importance. There is a fear of stifling production especially when no, or very little, causal (or correlative) proof of toxicological danger exists. Plus, most of

<sup>25</sup> See David Ozonoff, *The Precautionary Principle as a Screening Device*, in *Protecting Public Health and the Environment: Implementing the Precautionary Principle* (Carolyn Raffensperger & Joel Tickner eds., 1999).

<sup>26</sup> See Susan R. Poulter, *Monte Carlo Simulation in Environmental Risk Assessment: Science, Policy and Legal Issues*, 9 *Risk: Health, Safety & Environment* 7 (1998).

these actions are implausible because of the pervasive globalized use of some chemical substances (e.g., DDT).

Furthermore, such a drastic call to arms usually spurs political dissent, creating a hostile policy environment in which to negotiate alternative actions. This in turn raises legal concerns since most precautionary actions usually require some type of juridical intervention and support. The interface between science and law is a tenuous one at that, prone to misinterpretation and stagnation. Essentially, a procedural and statutory bias exists, often favoring preexisting operational practices of a possibly polluting activity.<sup>27</sup>

Even if precautionary actions are successfully initiated, they can be as time consuming as the original risk assessment. In fact, one could argue that ascertaining scientifically valid evidentiary data plus acquiring precautionary default limits while simultaneously addressing chronic toxicity and conducting a technology options assessment, as well as facilitating a meaningful open democratic dialogue between all stakeholders, would require even more time and resources than traditional quantitative risk assessment.

Scientists in a precautionary approach are members in a cooperative, multidisciplinary, problem-solving community, a community composed of ethicists, legislators, lawyers, labor and business representatives. A precautionary approach is a holistic undertaking that transcends traditional scientific boundaries. Peer review is an inclusive endeavor, drawing from a vast range of expertise in addressing an issue. Because a precautionary approach takes a long-range point of reference to human impacts on environmental health, and due to methodological and ethical complexities of such a temporal and geographical perspective, authentic problem-solving techniques are beyond the scope of any single scientific discipline. Shrader-Frechette and McCoy argue that isolated scientific disciplines' research methods, theories, and empirical bases in ecology are "underdetermined," and thus cannot provide a foundation for effective environmental policy formulation.<sup>28</sup>

<sup>27</sup> See Carl F. Cranor, *Asymmetric Information, the Precautionary Principle, and Burdens of Proof*, in *Protecting Public Health and the Environment: Implementing the Precautionary Principle* (Carolyn Raffensperger & Joel Tickner eds., 1999).

<sup>28</sup> See Kristin Shrader-Frechette & Earl D. McCoy, *Method in Ecology: Strategies for Conservation* (Cambridge U. Press 1993).

Thus, Barrett and Raffensperger conclude, “For such reasons, scientists must participate in research that is multidisciplinary (e.g., incorporates social sciences), multilevel (e.g., considers networks and relationships), and community based (e.g., includes many different value judgments).”<sup>29</sup> Essentially, by itself, a top-down, holistic approach to toxicological risk assessment is a time consuming and expensive endeavor fraught with political and social tension. Given the inherent limits of precautionary actions operating autonomously, an alternative approach or process is necessary to co-exist beside a precautionary attitude that will effectively ensure public health and ecological stability while still juggling all stakeholder interests and facilitating an open, democratic forum in which to allow relevant voices to be heard during the interim phase of a risk assessment.

### Short-Term Tests: Effectively Integrating Risk Assessment and Precautionary Attitudes

Currently, EPA intentionally uses default options intended to yield health-protective risk estimates absent sufficient data or resources to characterize each risk-assessment parameter accurately. Using an iterative approach to toxicological screening, lower-tier assessments can be used for preliminary screening relying heavily on pre-determined default options. Results of such screening support conservative, health-protective exposure limits.

If a lower-tier risk assessment indicates that an unacceptable health risk could be associated with a particular exposure or a regulated party believes that the risk has been overestimated, a higher-tier risk assessment can be performed. Instead of relying on default parameters, higher-tiered risk assessments use more precise technology, which is more time consuming and expensive but provides more accurate information. “Conversely, if EPA believes that a lower-tier risk assessment has underestimated the health risk associated with a particular exposure, a higher-tier risk assessment might yield a more reliable estimate.”<sup>30</sup>

<sup>29</sup> Katherine Barrett & Carolyn Raffensperger, *Precautionary Science*, in *Protecting Public Health and the Environment: Implementing the Precautionary Principle* 115 (Carolyn Raffensperger & Joel Tickner eds., 1999).

<sup>30</sup> See Committee on Risk Assessment of Hazardous Air Pollutants, *supra* n. 1, at 247.

By incorporating an iterative toxicity-screening paradigm through the use of lower-tiered testing procedures, testing times for carcinogen potency assessments, for example, could be dramatically reduced. Taking anywhere between 0.5 to 5 person years per substance, traditional carcinogen potency assessments using animal bioassays, although amazingly accurate, consume vast quantities of time and resources.<sup>31</sup> The animal bioassay for carcinogenic detection is very complex and very expensive scientific study, usually involving hundreds of rodents, which must be dosed with the test chemical for most of their lives. Unfortunately, because of these time-constraints, in the last century, uncounted multitudes of chemicals have been introduced into the environment with hundreds more being synthesized and distributed every year with only an alarmingly small percentage being tested with conventional animal studies.

Even as late as 1994, EPA's inventory of regulable chemicals under TSCA exceeded 72,000 substances, most of which had not been evaluated for basic toxicity screening.<sup>32</sup> With an ever-widening net of chemicals being brought into global production and distribution every year, traditional testing methods are just too time consuming and expensive to keep up with demand. With limited resources and budget, coupled with the financial burdens of conducting toxicological risk assessments, EPA's selective enforcement policy facilitates a less than lack-luster motivation for private industry to thoroughly evaluate the safety of their chemical products before they are released into the public.

For instance, the recent debate surrounding Methyl Tertiary Butyl Ether (MTBE), a fuel oxygenate in use since the mid-1970s, illuminates the dire importance for interim assessment. Heavily tested for human health effects relating to inhalation and air quality, MTBE underwent almost no testing to determine its effect on aquatic ecosystems and drinking water. Lacking sufficient data, both EPA and the National Science and Technology Council in 1997 reported they could not adequately estimate potential acute or chronic health risks of MTBE at low exposure levels in drinking water, even though it is widely known

<sup>31</sup> See Cranor, *supra* n. 9.

<sup>32</sup> General Accounting Office, GAO Report, B-256039, Toxic Substances Control Act: Legislative Changes Could Make the Act More Effective 2 (1994).

that MTBE is a human carcinogen.<sup>33</sup> Created to redress a public health hazard, MTBE itself inadvertently became a public health hazard precisely because of inadequate and non-holistic interim risk characterization and exposure analysis.

This lack of interim testing constitutes a major environmental and human health problem. When EPA began ranking human health risks associated with occupational exposures, pesticide residues, and hazardous waste sites, EPA's analysis was marred by the lack of assessments available for study. In fact, most state agencies rely on occupational exposure limits for screening and regulating toxic sources, which often lack threshold levels for toxic effects, and unfortunately, rarely are health-based. Even more troubling is that different agencies, operating with different datasets and regulatory schemas that generate different, and at times, contradictory sets of guidelines, many for the same compounds.<sup>34</sup>

For these reasons, the last several decades have seen a rise in the number of relatively cheap and rapid tests for detecting mutagenic and carcinogenic chemicals. Known as Short Term Tests (STTs), these procedures are economical resources that can function as screening devices capable of producing usable data usually in a matter of weeks. Most of these STTs are based on the demonstration of chromosomal damage, gene mutations, or DNA damage, with many of them being *in vitro* assays, meaning they are conducted in experimental biological systems without the use of live animals. The test organisms range from bacteria and yeasts to insects, plants, and cultured animal cells. In some instances, laboratory animals are exposed to test chemicals from periods typically ranging from a couple of hours to several weeks.<sup>35</sup>

<sup>33</sup> Committee on Environment and Natural Resources, National Science and Technology Council, *Interagency Assessment of Oxygenated Fuels* (June 1997).

<sup>34</sup> Sara M. Hoover et al., *Improving the Regulation of Carcinogens by Expediting Cancer Potency Estimation*, 15 *Risk Analysis* 2 (1995) (citing Science Advisory Board, *The Report of the Human Health Subcommittee: Relative Risk Reduction Project* (EPA SAB-EC-90-021B, Washington, DC, 1990); S.T. Dydek, *Comparison of Health Risk Assessment Approaches for Carcinogenic Air Pollutants*, Presented at 82nd AWMA Annual Meeting, Anaheim, CA (1989); Edward Calabrese & Elaina Kenyon, *The Perils of State Air Toxics Programs*, 23 *Environmental Science and Technology*, 1323 (1989)).

<sup>35</sup> See International Commission for Protection Against Environmental Mutagens and Carcinogens, *Guide to Short-Term Tests for Detecting Mutagenic and Carcinogenic Chemicals*, a report prepared for the International Programme on Chemical Safety, World Health Organization, Geneva, 1985.

Although less accurate than traditional testing methods, many STTs are sufficiently accurate for lower-tier hazard identification purposes. In fact, modeling procedures similar to those used by environmental economists suggest that even STTs that are less than fully accurate, with false positive rates above 0.05, may have uses both in premarket and in postmarket regulation situations.<sup>36</sup> Bacterial bioassays STTs, which are the most extensively studied and validated type of STT, have in one study given a predictive value for carcinogenic potential of about 90%.<sup>37</sup> For instance, a well-known bacterial (*Salmonella*) assay can screen chemicals for potential mutagenicity and carcinogenicity, as well as map mechanisms of toxic action, by evaluating a compound's ability to mutate DNA.<sup>38</sup>

STTs are not designed nor should be used for estimating the risk of a potential carcinogenic substance. Since STTs are less accurate and are prone to unique constraints, often because of their simplicity in design and use, STTs should be used in a series of "batteries," allowing for an opportunity to correlate and compare results through several trials.<sup>39</sup> As stated earlier, the question of quantifying risk is already an uncertain business, dependent upon many factors. Data gained from screening tests, such as STTs, cannot be used as the sole basis for predicting the potency of the carcinogenic activity in the environment or in humans. STTs merely act as preliminary indicators, pointing out which substances ought to receive priority for further, more extensive study.

Nevertheless, STTs still offer significant advantages over the traditional toxicological risk assessment paradigm. Lists of potentially toxic substances based on STTs could be used by academic institutions to help redress data gaps, expand the number of research institutes

<sup>36</sup> See Talbot Page, *A Framework of Unreasonable Risk in the Toxic Substances Control Act*, in *Annals of the New York Academy of Science: Management of Assessed Risk for Carcinogens* 145 (William J. Nicholson ed., 1981). See also Lester Lave & Gilbert S. Omenn, *Cost-Effectiveness of Short-Term Tests for Carcinogenicity*, 324 *Nature* 29 (1986).

<sup>37</sup> See J. McCann & Bruce N. Ames, *Detection of Carcinogens as Mutagens in the Salmonella/Mitrosome Test: Assay of 300 Chemicals*, 75 *Proc. Nat. Acad. Sci.* 5135 (1975); *Evaluation of Short-Term Tests for Carcinogens* (F. J. De Serres & J. Ashby, eds., (1981) *Progress in Mutation Research*, Vol.1).

<sup>38</sup> E. Zeiger, *Mutagenicity Tests in Bacteria as Indicators of Carcinogenic Potential in Mammals*, in *Environmental Mutagenesis* 107-19 (D. H. Phillips & S. Venitt eds., 1995).

<sup>39</sup> See International Commission for Protection Against Environmental Mutagens and Carcinogens, *supra* n. 35.

because of lower costs associated with testing, as well as confirm or refute preliminary toxicity data from industry or government sources.<sup>40</sup> STTs could be used by public watchdog organizations, or by industry itself, to quickly assess the potential carcinogenic properties associated with a particular substance.

In a regulatory context, STTs could be mobilized in an iterative testing paradigm, as a lower-tiered screening program, to trigger more expensive and time-consuming risk assessments. This would allow for more streamlined regulatory hurdles, increasing industry compliance and accountability. STTs create market-based incentives for improved product performance by providing for greater regulatory transparency and accountability, broadening the number of third party testing agencies, and increasing the potential frequency of governmental audits of a company's compliance performance.

There are also unique social and ethical advantages to using STTs, particularly when discussing issues regarding research conducted on laboratory animals. Public concern about animal use in the past several decades has resulted in the enactment of several legislative mandates requiring scientists to consider, prior to *in vivo* research, alternatives that either do not use animals, significantly reduce the number used, or minimize pain and distress.<sup>41</sup> Currently there are a series of alternative *in vitro* cytotoxicity tests that show promise of either replacing or reducing rodent acute oral toxicity tests for determining LD50 values. If properly developed and refined, such *in vitro* methods could ultimately replace the use of laboratory animals in acute lethality tests.<sup>42</sup> For instance, a recent National Institutes of Health report cites a previous study describing the *Limulus* Amebocyte Lysate test, a time and cost-saving *in vitro* method using blood cells from horseshoe crabs, which has replaced rabbit pyrogenicity testing to detect endotoxins.<sup>43</sup>

<sup>40</sup> See Cranor, *supra* n. 27.

<sup>41</sup> Such legislation includes Animal Welfare Act., Pub. L. No. 99-198; Health Research Extension Act of 1985, Pub. L. No. 99-158; NIH/National Institutes of Health Revitalization Act, Pub. L. No. 103-43.

<sup>42</sup> National Institute of Environmental Health Sciences, Report of the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity, National Institutes of Health (NIH) Publication No. 01-4499, 29 (2001).

<sup>43</sup> NIEHS (National Institute of Environmental Health Sciences), Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods, NIH Publication No. 97-3981



Although this is probably unlikely in the foreseeable future, many in vivo STTs can use phylogenetically lower organisms such as fish, invertebrates, and algae, to test for environmental effects in assessing ecotoxicity, as well as potential carcinogenic danger, of many ubiquitous chemicals.

Furthermore, expedited potency assessments, which are often procedural programs designed to increase the efficiency of risk assessments, can also function much like STTs. For instance, the Linearized Multistage Default Method (LMS), utilizing the Carcinogenic Potency Database (CPDB) created by Lois Gold et al.<sup>44</sup>, streamlines several procedural actions and facilitates several tasks that under traditional risk assessments are extremely time consuming.<sup>45</sup> Through LMS paradigm potency, values are quickly estimated using default risk extrapolation procedures adopted by EPA and CEPA (California Environmental Protection Agency). CEPA used LMS to estimate the carcinogen potency for 200 agents in an eight-month time period (compared to only 70 in the previous five years) as part of California's enforcement of its Proposition 65 (Safe Drinking Water and Toxic Enforcement Act of 1986).<sup>46</sup> Had traditional science-intensive carcinogen potency assessments been used on the same 200 agents, the cost would have been between \$7 million and \$70 million. As it stands, the use of LMS reduced this estimated cost to a mere \$4,000.<sup>47</sup>

As illustrated by LMS and other testing procedures, STTs provide inherent advantages over traditional approaches to risk assessment or strict precautionary action. In fact, when used in an iterative interim risk characterization program, STTs bridge the gap between the normative and social responsibilities of conducting a toxicological risk assessment

(1997)(citing Oliver P. Flint, *A timetable for replacing, reducing and refining animal use with the help of in vitro tests: The Limulus Amebocyte Lysate Test (LAL) as an example*, in *Alternatives to Animal Testing: New Ways in the Biomedical Sciences, Trends and Progress* 27-43 (C.A. Reinhardt ed., (1994)).

<sup>44</sup> Lois Swirsky Gold et al., *A Carcinogenic Potency Database of the Standardized Results of Animal Bioassays*, 58 *Envtl. Health Persp.* 9 (1984).

<sup>45</sup> See Hoover et al., *supra* n. 34.

<sup>46</sup> Reproductive and Cancer Hazard Assessment Section, California Environmental Protection Agency, *Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens* (1992) (cited in Cranor, *supra* n. 27).

<sup>47</sup> See Cranor, *supra* n. 9, at n. 10.

and the necessity of upholding a “sound science” approach to accurately determining the potential threat of a substance. Because STTs still operate within the “scientific paradigm,” they require less of a pragmatic and theoretical confrontation between traditional risk assessment adherents and Precautionary Principle advocates. STTs used during the interim phase of a risk assessment are not meant as definitive statements of the toxicological danger of substance, but rather act only as preliminary indicators warning of a potential public health or ecological hazard.

In conclusion, conceiving of risk assessment, in part, as a mechanism for protecting public health and environmental safety, opens up the possibility of different evidentiary approaches for different informal and regulatory purposes—just as we otherwise demand different kinds and amounts of evidence in different social and legal contexts.<sup>48</sup> A greater onus should be placed on creating and implementing STTs in conjunction with a precautionary attitude during the interim phase of toxicological risk assessments that use iterative, conservative, tiered procedures. In this way, social costs will be minimized, while the scientific and normative rigor necessary to validate conclusions will be preserved. And in this way, the process will remain flexible enough to incorporate uncertainty and public input into the matrix of protecting public health and ecological integrity.



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48 *Id.*

