ADVANCING THE NEXT GENERATION OF RISK ASSESSMENT : A NEXGEN PROGRAM SYNOPSIS

The landscape of risk assessment is changing to an extent that significant transformation is necessary. The changes are largely being driven by phenomenal advances in medicine and molecular systems biology[1], the advent of several significant reports from the National Research Council (NRC), and compilation of volumes of new test data from Tox21[2] and Europe.[3] The European data alone will soon create the need for thousands of de novo risk assessments.

These events are prompting us to look at risk assessment in new ways, to position EPA for the future, and to contribute meaningful change to the risk assessment and risk management communities. Hence, we are embarking on an exploration of new science and methods to incorporate into emerging and future risk assessments. The program is entitled "Advancing the Next Generation of Risk Assessment (NexGen)." This effort is embodied in a collaborative program among the Environmental Protection Agency; National Institutes of Environmental Health Sciences/National Toxicology Program; National Human Genome Research Institute; Centers for Disease Control/Agency for Toxic Substances Disease Registry, and the State of California's Environmental Protection Agency. The initial 18 months focuses on health assessment, while a second phase will focus on exposure assessments.

NexGen is a component of a larger effort – Safer Product for a Sustainable World Initiative (SPSW) and is focused on risk assessment applications of new methods:

SPSW Problem Statement. Although chemicals are essential to modern life, we lack innovative, systematic, effective, and efficient approaches and tools to inform decisions that reduce the environmental and societal impact of chemicals while increasing economic value.

SPSW Vision. EPA science will lead the sustainable development, use, and assessment of chemicals by developing and applying integrated chemical evaluation strategies and decision

NexGen will guide health assessment procedures within NCEA, which is responsible for developing assessments to support decision-making and risk management for EPA's Air, Water, and Superfund, and Emergency Response programs. It will also support SPSW efforts. This evaluation of the latest science is anticipated to significantly advance the field of risk assessment and to have broad interest.

The NexGen Program

Advances in molecular systems biology are revealing just how complex and variable biologic processes within the human population are. This rapidly evolving knowledge highlights the multifaceted nature of disease processes and susceptibilities to induction or modifications.

NexGen's goal is to incorporate this emerging knowledge into risk assessment. Through iterative development of the next generation of risk assessments, NexGen will create first approximations, learn from

[1] This term encompasses, but is not limited to, genomics, proteomics, epigenetics and metabolomics.

[2] Tox21 is collaboration among several US federal agencies to modernize toxicity testing and is testing 10,000 chemicals in the next 5 years (www.epa.gov/ncct/Tox21).

[3] REACH is a new European Community Regulation on chemicals and their safe use (EC 1907/2006). It deals with the **R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emical substances. The aim of REACH is to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. 120,000 chemicals have been preregistered for consideration.

these efforts, and then refine the next versions based on this new knowledge. The development of new prototypes will serve as the fundamental basis for examining proof of concepts, assessing the value of new information, and developing decision rules for use of new information.

The specific objectives of NexGen:

1. Pilot implementation of the NRC Framework for Risk Based Decision-making,[4] including characterizing risk management needs, identifying policy-relevant questions and risk assessment implications, and defining stakeholder involvement.
2. Refinement of bioinformatics systems for knowledge mining and creation to serve risk assessment.
3. Development of prototype health assessments that respond to the context of risk and can be refined through discussions with scientists, risk managers, and stakeholders.

Prototypes will focus on extensive evaluations of high-throughput/high-content bioassay data for some of the most well-characterized chemicals. A broad set of questions we seek to address is shown in the text box to the right. In essence, we will try to "reverse engineer" assessments based on the new types of data to existing, robust, in vivo data-based health assessments. As a premium is placed on knowledge of risks derived from human in vivo data, this approach will provide a way to evaluate the utility of the new types of data against the best available traditional data.

A broad set of questions to address

- Can these new data and methods improve our understanding of risk in valuable ways?
- What newly available data and knowledge are not included in current health assessments but potentially should be?
- How can this new type of information best be incorporated into health assessments and used to inform risk managers and the public?
- What new policies and procedures are needed?
- How can we ensure that the redesigned process is scientifically robust, consistent across assessments, and matched to the risk context?

To the extent data and time allow, the effort will focus on the utility of toxicity pathways and networks in identifying potential adverse effects, evaluating the role of qualitative and quantitative predictors of response, and studying human variability/susceptibility, backgrounds of exposure and disease, and mixtures. Initially, we will evaluate three diseases/disorders, and a two or more associated chemicals for each category (see Table 1 below). For simplicity, each prototype will initially be limited to a subset of the underlying mechanism of action. Table 1 shows disorders/diseases and chemicals under consideration (short and long term), and underlying specific mechanisms of action under consideration for these prototypes, and other relevant details.

Implications for Risk Assessment

By incorporating emerging molecular systems biology knowledge, NCEA anticipates implementing a new tiered health assessment paradigm. This new paradigm is aimed at creating health assessments that are more responsive to the needs of program offices, including the ability to cost effectively and more rapidly assess chemicals. Figure 1 illustrates three envisioned risk assessment tiers. Consistent with NRC recommendations (NRC 2009), this paradigm facilitates assessments with differing attributes that can be more responsive to the risk context and decisions that consider risk assessments. Tier 1 (far left) focuses on screening and ranking of thousands of chemicals and depends on high throughput assays and quantitative structure activity relationships (QSARs). Tier 2 (middle) focuses on narrow-scope assessments of hundreds of chemicals and is high throughput/QSAR reliant, augmented with high content assays and selected traditional data. Tier 3 focuses on broad, very detailed assessments of a few chemicals (dozens), using as much policy-relevant, emerging, and traditional data as is feasible. These complex Tier 3 assessments are reserved for

[4] As articulated in its report, *Science and Decisions: Advancing Risk Assessment*.

situations of greatest concern—highest hazard and public exposure. Although the three tiers are represented in Figure 1 as discrete boxes, in practice, these approaches lie on a continuum of risk assessment tools.

Table 1: Possible Prototype Risk Assessments Organized by Disease/Disorder

	Respiratory Toxicity	Endocrine Disruption		Cancer
		Androgen	Thyroid	
Chemicals Under Consideration for Initial Prototype	Ozone, chlorine	Dibutyl phthalate	Bisphenol A, perchlorate	Benzo(a)pyrene and other polycyclic aromatic hydrocarbons (PAHs); benzene, conozoles
Other related chemicals under consideration	Aldehydes, particulate matter, sulfur and nitrogen oxides, phosgene, peroxyacetyl nitrate	Other biomonitored phthalates, other AH disruptors	PBDE, other biomonitored TH disruptors	Other mutagenic carcinogens
Disease/Disorder	Lung injury and related respiratory diseases	Testicular dysgenesis - reproductive dysfunction - fetal germ cell effects - malformations	Neuro-developmental impairment	Cancer
Mechanisms of Action	Inflammation Airways reactivity	↓ Testosterone ↓ insl3	↓ Thyroid hormones	DNA reactivity Gene mutation
Sensitive Subopulations	Asthmatics, children	Fetuses	Fetuses, children	Fetuses (?), children
Exposure Pathways	Air	Air, soil, water, food	Air, soil, water, food	Air, soil, water
Exposure Issues	Dose rate, intermittent exposures, co-exposures			
Other Stressors	Allergens, preexisting disease	Other antiandrogens, preexiting disease	Other disruptors, preexisting disease	Other mutagenic carcinogens, preexisting disease

Figure 1: Risk Assessments Responsive to Risk Context – Three Proposed Tiers