A Literature Review of Emerging Technologies and Strategies for Reducing Uncertainty and Increasing Accuracy and Efficiency in Environmental Risk Assessment

By

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Biography

Michael Beuthe grew up in Holmdel, NJ and received his bachelor of science degree in biology from Fairleigh Dickinson University in 2010. Upon graduating from Fairleigh Dickinson, Mr. Beuthe briefly worked at Duke Farms as an Environmental Technician, before joining the crew of the NJ tall ship, the AJ Meerwald, where he taught marine education to elementary school students aboard the ship. Mr. Beuthe began working in the Environmental Consulting industry in 2011. During the past five years, Mr. Beuthe has worked for Weston Solutions, Inc., where he provides support to the EPA during the assessment and cleanup of CERCLA regulated sites in New Jersey, New York, Puerto Rico and the Virgin Islands. His work also includes providing support to the EPA during emergency responses. In his free time, Mr. Beuthe enjoys working out, trying new foods, cooking, and spending time with friends and family.
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Executive Summary

A literature review was conducted to assess the uncertainty and limitations associated with the current environmental risk assessment paradigm: toxicity assessment, exposure assessment, and risk characterization. The goal was to identify and summarize emerging techniques and strategies to reduce uncertainties and limitations. Furthermore, the potential of emerging technologies and strategies to change the risk assessment paradigm were also evaluated. The literature review included primary literature and various guideline documents from regulatory bodies. The main focus topics included toxicology, molecular biology, genetics, remote sensing geographical information sciences (GIS), nano technology, chemical sensors, computational modeling and biomonitoring. Review of this extensive literature indicates that emerging techniques and strategies in toxicity assessment should focus on replacing toxicity data from controlled animal laboratory studies using high doses and apical end points with human toxicity data based on toxic end points associated with lower chronic doses which are more typical of environmental exposure to toxicants. Emerging strategies and techniques that can meet this objective include cytotoxicity data obtained from in vitro high throughput screening (HTS) of human cell lines exposed to low doses of environmental toxicants, and physiologically based pharmacokinetic (PBPK) models and virtual tissues (VTs) to evaluate in vitro data to in vivo conditions and determine internal dose with more accuracy than current methods. In parallel, exposure assessment should focus on replacing exposure estimates based on limited sampling, monitoring and exposure factor data with methods that will provide near-real-time exposure concentrations on finer spatial scales, and track receptor-specific exposure frequency and duration in both indoor and outdoor locations. Emerging techniques and strategies to meet this objective include the ubiquitous deployment of light weight, low cost nano-electro and micro-electro chemical sensors capable of measuring near-real time exposure concentrations at much finer resolutions, and advances in geospatial analyses to estimate exposure concentration in unmeasured locations. The use of publicly accessible online monitoring networks to upload, share and view exposure data will potentially make it easier to identify and mitigate areas of concern, and may eventually change the exposure assessment process from a strictly scenario-based process to one that is more holistic. Developments in tracking technologies will provide environmental risk assessors with more accurate and receptor-specific data in regard to exposure frequency and duration, and developments in portable and easy to use biomonitoring technology such as lab-on-a-chip will provide a method of obtaining biomarkers directly from populations in areas where the use of less invasive methods identify an exposure of concern. Lastly, it is anticipated that the full implementation of the emerging strategies and techniques will be a gradual process, and that an environmental “tool box” or similar system should be developed to provide an easy to use resource for risk assessors who are interested in using new risk assessment techniques during this transition process but lack the time and resources to thoroughly search through all of the new emerging techniques and strategies.
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Acronyms and Abbreviations
ABM – agent-based modeling
ADME - absorption, distribution, metabolism, and elimination
AML – acute myeloid leukemia
AOD – aerosol optical depth
AOP – adverse outcome pathway
AOT_{40} - Above Ozone Threshold of 40 ppb
AP – access network
BCI - biophysical composition index
BE – biomonitoring equivalent
BMDL_{10} - Bench Mark Dose lower limit of the 95% confidence interval
CDC – Center of Disease Control and Prevention
CERAPP - Collaborative Estrogen Receptor Activity Prediction Project
CSF – cancer slope factor
EC_{10} - effective concentration, 10th percentile
EC_{20} - lowest concentration that induces a 20% effect
EC_{50} – lowest concentration that induces a 50% effect
EGEE - ethylene glycol monoethyl ether
EGME - ethylene glycol monomethyl ether
EPA – U.S. Environmental Protection Agency
ER – estrogen receptor
ERS – Environmental Risk Score
EVI – enhance vegetation index
FDA – Food and Drug Administration
GIS – geographical information science
GOES - Geospatial Operational Environmental Satellite
GPS – geographical positioning system
GSM - global systems for mobile
HDL - high-density lipoprotein
HHRA – human health risk assessment
HI – hazard index
HQ – hazard quotient
HTS – high throughput screening
IDW – inverse distance weighted
LADD – lifetime average daily dose
LCLs - lymphoblastoid cells
LDL - low-density lipoprotein
LOAEL – lowest observed adverse effect level
LOED - lowest observed effective dose
LSWI - land surface water index
LUR – land use regression
ME – microenvironment
MF – modification factor
MODIS - Moderate Resolution Imaging Spectroradiometer
NASA - National Aeronautics and Space Administration
NDVI - normalized differential vegetation index
NER - National Reports on Human Exposure to Environmental Chemicals
NHANES – National Health and Nutrition Examination Survey
NHEAS - National Human Exposure Assessment Survey
NIH – National Institute of Health
NOAA - National Oceanic and Atmospheric Administration
NOAEL – no observed adverse effect level
NPEs - nonylphenol ethoxylates
NRC – National Research Council
OSHA - U.S. Occupational Safety and Health Administration
PBPK - physiologically based pharmacokinetic
PCB – polychlorinated biphenyls
PEL – permissible exposure limit
PM10 - particulate matter less than 10 microns
POD – point of departure
ppb – parts per billion
ppm – part per million
QSAR – quantitative structure activity relationship
RBF – radial base function
RfC – reference concentration
RfD – reference dose
SATVI - soil-adjusted total vegetation index
SAVI - soil adjusted vegetation index
SEM – scanning electron microscope
SNP – single nucleotide polymorphism
SPOT - Satellites Pour l’Observation de la Terre
SWCNTs - single walled carbon nanotubes
TSM – total suspended matter
TVI - transformed vegetation index
UF – uncertainty factor
USGS - United States Geological Survey
VOC – volatile organic compound
VOCC - Voltage operated Ca2+ channel
VT – virtual tissues
WDVI - weighted difference vegetation index
WPS - Wifi positioning system
1. Introduction

Unintended exposure to toxicants has been a concern throughout human history. Initially, this concern was based on toxicants that were purposely introduced into products for beneficial reasons such as pesticides, preservatives, and pharmaceuticals. Thus, the goal of early toxicity testing was to determine if the toxicant being tested presented unreasonable risk to human health outweighing any benefit associated with the addition or use of the toxicant. However, by the late 1960s, there was growing public concern about exposure to environmental toxicants that presented unreasonable side effects to those who were exposed, including both human and the environmental receptors (NRC, 2007). This concern was different than previous concerns of pesticides, food additives, or drugs, because these environmental contaminants were waste products that were introduced into the environment through irresponsible (and often unregulated) disposal practices rather than chemicals that were being intentionally introduced to a product for beneficial purposes. In addition, these environmental contaminants were present in heterogeneous environments (e.g., water, soil) at varying concentrations that were capable of producing acute, and/or chronic health effects following exposure to humans or other organisms. With the increasing need for toxicity testing to generate data capable of evaluating multiple exposure scenarios to a growing variety of chemicals and chemical mixtures, it became apparent that a more streamlined and consistent process was needed. In 1983, The National Research Council (NRC) identified such an approach in their 1983 report Risk Assessment in the Federal Government: Managing the Process. This report presented a systematic and organized paradigm that set the standard for human health risk assessments (HHRA). The report identified a three-phase process that incorporated toxicity data generated in the laboratory or field (research phase) into the risk assessment process (risk assessment phase), and then onto decision makers and stakeholders to determine the appropriate regulatory and mitigation options (risk management phase) (NRC, 2007).

The HHRA for exposure to environmental toxicants (i.e. environmental risk assessment), herein referred to as “risk assessment” consists of identifying the hazard posed by an environmental toxicant, then quantifying the potential risk posed by that hazard based on exposure conditions (Connell, 2005). The goal of a risk assessment is to determine the probability that a toxicant will cause adverse health effects to receptors under current or predicted (i.e., prospective risk assessment) exposure conditions. The process typically combines data obtained in the field through environmental sampling and monitoring, with toxicological literature and information on local human receptors and environmental resources to characterize the risk posed by the environmental toxicant. The risk assessment process is typically divided into three parts: 1) toxicity assessment, which can be subdivided into hazard identification and dose-response assessment, 2) exposure assessment, and 3) risk characterization. During hazard identification, adverse effects of an environmental toxicant are identified using data obtained from toxicity studies, or through mode of action, or weight of evidence approaches. The dose-response assessment uses toxicity information identified during the hazard identification to quantitatively characterize the relationship between the exposure dose of an environmental toxicant that is associated with an adverse effect to determine the no-observed adverse effect level (NOAEL) or a similar point of departure (POD) which is subsequently used to calculate the reference dose (RfD) [or reference concentration (RfC) for airborne toxicants] for non-carcinogens. The RfD and RfC are essentially the quotient of the POD identified in the dose-response assessment and the product of various uncertainty factors (UFs) and modification factors (MFs) which are discussed in more detail in subsequent sections of this review. Refer to equation 1.1 for an example of an RfD or RfC equation and Figure 1.1 for a depiction the NOAEL, lowest observed adverse effect limit (LOAEL) and POD on a dose-response curve.

\[
RfD \text{ or } RfC_t = \frac{\text{NOAL or LOAEL}}{\text{UFs} \times \text{MFs}}
\]

Equation 1.1
When evaluating carcinogens during the dose-response assessment, a cancer slope factor (CSF) is calculated using data from the hazard identification step. This term has recently been updated to cancer potency slope, however the former term, CSF, will be used throughout this review. During an exposure assessment, the intake dose of an environmental stressor by site receptors (e.g., residents, workers, farmers) is estimated using site information, receptor exposure information (e.g., frequency of site use, duration of site use, biometric factors, etc.), and physical chemical properties of the environmental toxicant. An exposure assessment typically begins by determining the concentration of a particular toxicant within an environmental medium or multiple environmental media (e.g., soil, water, air), and ends with an estimate of the toxicant dose that is received by a nearby receptor. The final dose estimate is highly dependent on both the physical and chemical properties of the contaminant which ultimately determines its environmental fate and transport, and multiple receptor exposure factors including but not limited to age, body size, time activity patterns, behavior patterns, gender, and genetics. Several statistical models are used to develop site-specific characterizations of fate and transport, and receptor exposure factors when developing dose estimates during an exposure assessment. An exposure pathway is not considered “complete” until a source, pathway, exposure, and receptor are identified. “Incomplete” exposure pathways can generally be removed from further analysis. Intake doses can be calculated for acute, sub-chronic and chronic exposure scenarios. When evaluating a toxicant for carcinogen effects, lifetime average daily doses (LADD) are typically calculated, due to the chronic nature of cancer development. The final step is risk characterization. During this step RfDs or CSFs, obtained during the dose-response relationship are combined with the intake doses obtained during the exposure assessment step, to calculate a hazard quotient (HQ) for non-carcinogens, and probability of cancer incidences for carcinogens. The hazard quotient is the quotient of the intake dose that
was estimated during the exposure assessment, and the RfD or RfC that was calculated during the toxicity assessment. A HQ that exceeds one typically represents an unacceptable risk. (See equation 1.2).

\[
D_{pot} = \frac{C \times IR \times ED \times EF}{BW \times AT}
\]

Equation 1.2

where

- \( D_{pot} \) – Potential dose
- \( C \) – Concentration of toxicant in environmental media (soil, water, air or food)
- \( IR \) – Ingestion Rate/Inhalation Rate (replaced by surface area and absorption coefficients when evaluating dermal routes of entry)
- \( ED \) – Exposure Duration
- \( EF \) – Exposure Frequency
- \( BW \) – Body Weight
- \( AT \) – Averaging Time (Replaced by life time for chronic exposure assessments)

The CSF obtained in the dose-response assessment is typically multiplied by the LADD to determine lifetime cancer risk. A lifetime cancer risk exceeding 1 in a million (1x10\(^{-6}\)) typically represents an unacceptable risk. (Refer to Table 1.1 for a summary of the risk assessment process).

There are many sources of uncertainty associated with the current risk assessment process. Many of these uncertainties are associated with the current methods that are utilized to collect and generate the data that are used throughout the risk assessment. With regard to data collection, current data uncertainties can broadly be classified into two categories: Uncertainty generated from using non-representative toxicity data in the toxicity assessment, and uncertainty from not accurately characterizing receptor and environmental variability during the exposure assessment. The current risk assessment process typically relies on data from high dose, acute exposure, laboratory animal studies to derive human toxicity levels associated with low doses over sub-chronic and chronic exposures. In addition, the current exposure assessment relies on many default values for parameters associated with both human exposure factors throughout the exposure assessment process (EPA, 1992). Recent advances in toxicity testing strategies, and environmental and biological monitoring technology show promising potential for generating data that can dramatically reduce uncertainty and increase the accuracy and efficiency of a risk assessment.

The goal of this project is to describe methods that are currently used to generate data during the risk assessment process and the limitations and uncertainty associated with data generated by those methods. Emerging technologies with the potential to replace each of the current methods discussed will be identified, followed by an explanation of how the implementation of each emerging technology will generate data that decreases uncertainty, while increasing accuracy and efficiency within the risk assessment process. Lastly, the potential of emerging technologies and strategies to change the risk assessment paradigm will be evaluated.
Table 1.1 - Summary of the Risk Assessment Process

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Identification</td>
<td>Adverse effects of the environmental toxicants are identified reviewing existing literature, using toxicokinetic, toxicodynamic, mode of action, or weight of evidence approaches.</td>
</tr>
<tr>
<td>Dose-response Assessment</td>
<td>Toxicity information is used to quantitatively characterize the relationship between the exposure dose of an environmental toxicant and the associated adverse effects to determine the NOAEL, RfD (or RfC for airborne toxins) for non-carcinogens, and CSF for carcinogens.</td>
</tr>
<tr>
<td>Exposure Assessment</td>
<td>Intake dose of environmental toxicants by site receptors is quantified using site information, receptor exposure information, and physical chemical properties of environmental toxicants. Both environmental sampling and statistical modeling are methods typically used during the exposure assessment.</td>
</tr>
<tr>
<td>Risk Characterization</td>
<td>RfDs or CSFs, obtained during the dose-response relationship are combined with the intake doses obtained during the exposure assessment step, are used to calculate a hazard quotient for non-carcinogens, and probability of cancer incidences for carcinogens.</td>
</tr>
</tbody>
</table>

2. Overview of Current Risk Assessment Method

The following sections summarize the current risk assessment method and discuss the current techniques and strategies that are used during both the toxicity and exposure assessment. The first step in the current risk assessment process is the hazard identification portion of the toxicity assessment, where the potentially adverse effects of a toxicant are identified. Current techniques and strategies used to identify adverse effects include evaluation of epidemiological, controlled human clinical, and controlled laboratory animal studies. Data from these studies are subsequently used in the dose-response portion of the toxicity assessment to quantitatively determine the relationship between the exposure dose of an environmental toxicant and the associated adverse effects by determining the POD, and calculating the RfD, and the CSF. Strategies and techniques used during dose-response include determining a non-linear POD from the dose-response curve produced by the data from the hazard identification step and using various MFs and UF s to obtain a conservative and protective RfD or RfC. When determining the CS F, low dose extrapolation models are used to extrapolate the acute, non-linear, high doses from the study to linear data associated with the chronic, low doses that are typically associated with cancer development in human receptors. Following the toxicity assessment, the exposure assessment is conducted. During the exposure assessment, techniques and strategies, including direct measurement of exposure at point of contact, estimates of exposure through scenario evaluation, and exposure estimation by reconstructing internal dose are used to determine the exposure concentration, potential dose, applied dose, internal dose, and target dose that is received by receptors that are exposed to the toxicant of concern.

There are several limitations and uncertainties associated with each of the previous mentioned steps of the current risk assessment process. Limitations and uncertainties with the hazard identification portion of the toxicity assessment include resolving differences that may exist amongst multiple studies for the same environmental toxicant and applying data and results from controlled human clinical and animal laboratory studies with controlled and homogenous exposure parameters to real world exposure scenarios that are well beyond the conditions and parameters in which the study was conducted. This application of data and results
from controlled human clinical and laboratory animal studies generates additional uncertainty in the dose-
response portion of the toxicity assessment where RfD and CSF calculations require extrapolations to be
made between the exposure parameters in the controlled human clinical or animal laboratory studies and
real-world exposure scenarios. Additional uncertainty in the current dose-response method exist when using
controlled laboratory animal studies, and accounting for physiological differences between laboratory
animals and human receptors. Another source of uncertainty in the current dose-response methods is the
inability to capture individual differences that may make receptors more or less susceptible to a particular
toxicant at different exposure levels, including differences in genetics, age, and pre-existing conditions.
Limitations and uncertainties in the current exposure assessment are associated with the static nature of the
current methods where exposure concentration is based on sampling, monitoring and modeling at a static
time and location, and typically uses limited exposure factor data that does capture the full heterogeneity
of the exposed population.

2.1. Toxicity Assessment
The toxicity assessment generally consists of two steps: hazard identification and dose-response
assessment. During the hazard identification step, information from epidemiological, controlled human
clinical, and controlled animal laboratory studies are evaluated to determine the potential adverse effects of
exposure to a particular toxicant. A single study is typically used when evaluating non-carcinogens, and
multiple studies are used in a weight of evidence approach when evaluating carcinogens. Data from the
hazard identification step is subsequently used in the dose-response step to quantitatively characterize the
relationship between the exposure dose of a particular environmental toxicant and the associated adverse
effects identified in the hazard identification step. During the dose-response step, dose-response data from
the critical study, or from multiple studies in the weight of evidence approach, are used to determine the
POD. The POD value is then used along with the appropriate extrapolations and/or MFs and UFs to
calculate the RfD (or RfC for airborne toxicants) for non-carcinogens, and CSF for carcinogens.

2.1.1. Hazard Identification
The goal of the hazard identification step is to determine and identify any adverse effects associated with
human exposure to a particular toxicant. Common sources that are used to identify adverse effects
associated with human exposure to a particular toxicant include: epidemiological studies, controlled human
clinical studies, and controlled laboratory animal studies (EPA, 1989). Depending on the particular toxicant,
limited or robust data may be available for evaluation during hazard identification. Typically, a single study
(termed the “critical study”) is used to generate toxicity data which are used throughout the toxicity
assessment when evaluating non-carcinogenic effects. The critical study is identified after all available
studies examining the toxicity of the particular environmental toxicant have been evaluated (EPA, 1989).
The study that is selected as the critical study is typically the study which evaluates the most sensitive toxic
endpoints. If human data are available, that information is used as the critical study (EPA, 1989). In absence
of human data, information from controlled animal studies are used instead with preference toward studies
that use animal models that are the most relevant to humans (EPA, 1989). When evaluating carcinogenic
effects, multiple studies and supporting data associated with tumor incidences in human and animal
receptors are evaluated using a weight of evidence approach to determine the likelihood that exposure to a
toxicant can cause cancer (EPA, 2005). The results of the weight of evidence classification are typically
presented in some type of ranking system where a particular toxicant is assigned a standard descriptor based
on its likelihood to cause cancer. For example, the current U.S. Environmental Protection Agency (EPA)
weight of evidence classifications use five categories to define the cancer risk associated with a particular
stressor: Carcinogenic to Humans, Likely to Be Carcinogenic to Humans, Suggestive Evidence of
Carcinogenic Potential, Inadequate Information to Assess Carcinogenic Potential and Not Likely to Be Carcinogenic to Humans (EPA, 2005). Multiple studies are evaluated in a weight of evidence approach.

Currently, controlled human clinical studies are considered to be the most reliable form of toxicity data. This reliability is attributed to the ability of the assessor to obtain toxicity data associated with human receptors in controlled environments. Therefore, any toxicity end points that occur during the study as well as any effects on metabolism and elimination can be more accurately evaluated when compared to using data from controlled animal laboratory studies. The second most reliable source of toxicity data is data obtained from epidemiological studies. Like controlled human clinical studies, the reliability of epidemiological studies can be attributed to the use of toxicity data associated with human receptors. However, unlike controlled human clinical studies, epidemiological studies examine human subjects in uncontrolled, “real-world” exposure scenarios which can produce variation and uncertainty in regards to exposure magnitude, frequency and pattern. Therefore, most data that are generated from an epidemiological study are considered observational data in which a statistical relationship can be inferred, but a causal relationship cannot be evaluated unless additional data related mechanistic information are available (NRC, 2009). Although human clinical studies are considered the most reliable, there are still several sources of uncertainty with toxicity data generated from these studies. In many cases, human clinical studies are based on exposures of a small number of participants to a single agent over a defined time period. Therefore, applying these data to a large heterogeneous population with inter- and intra-individual variations in exposure factors will produce some level of uncertainty. Although studies that use human toxicity data are generally considered the most reliable, the majority of toxicity data used throughout the toxicity assessment still come from controlled animal laboratory studies where homogenous groups of animals are exposed to high doses of a particular agent (NRC, 2007). The use of data from controlled animal studies to generate human toxicity data requires the assessor to extrapolate data associated with studies of homogenous animal populations exposed to doses, and at durations that are often not encountered in a more heterogeneous human population. Under the current risk assessment paradigm, basing the toxicity assessment on data obtained from animal studies triggers the use of uncertainty factors (UFs) usually in multiples of 10 in the RfD/RfC calculation. In addition, modification factors (MFs) are added to the equation to account for professional assessment of additional uncertainties in the critical study, and the corresponding toxicity data that are not addressed by the preceding UFs (EPA, 1989). (Refer to equation 1.1).

Two UFs typically associated with toxicity assessments that rely on animal studies are (1): a UF of 10 for interspecies extrapolation and (2): a UF of 10 when an acute or sub-chronic study is used to develop chronic toxicity values (EPA, 1989). An additional source of uncertainty in the hazard identification is evaluating and resolving differences that may exist amongst multiple studies for a particular agent. These differences may be related to different toxicity values obtained from similar studies examining the same toxic end point, or they may be the result of studies that examine two different toxic end points. An example of the latter situation occurred in a 2002 NRC review of a draft EPA RfD for oral exposure to perchlorate. EPA based its RfD calculation on a study that evaluated brain morphometry (i.e. measurements of brain structures), thyroid histopathology, and serum thyroid-hormone concentrations in rats as toxic endpoints. In contrast, NRC used an epidemiological study evaluating the inhibition of iodine uptake by the thyroid in a small group of healthy exposed human subjects (NRC, 2009). As a result, NRC obtained an RfD of 0.0007 mg/kg per day; 23 times larger than the EPA’s draft RfD of 0.00003 mg/kg per day (NRC, 2009). The NRC RfD therefore was seemingly less protective than that obtained by EPA even though it used a study with lower exposure doses, and a potentially more sensitive toxicity end point. However, further evaluation reveals that this difference in the RfD value can be attributed mainly to the use of a higher UF (300) used by EPA compared to an UF of 10 used by the NRC. This example demonstrates how the use two different studies
during the hazard identification step can alter the final toxicity values that are generated at the end of the
toxicity assessment and why it is so critical to understand the underlying assumptions calculations applied
for each study. Section 3 of this paper will identify several new methods in toxicity assessment which have
the potential produce RfD values with more accuracy and eliminate or significantly reduce the use of UFs.

2.1.2. Dose-Response Assessment
Following hazard identification, toxicity data from the critical study is used in the dose-response assessment
to quantitatively characterize the relationship between the exposure dose of an environmental toxicant and
the associated adverse effects to determine the POD and calculate the RfD (or RfC for airborne toxicants)
for non-carcinogens, and CSF for carcinogens. When evaluating an agent for non-carcinogenic effects, a
non-linear POD is identified from the dose-response curve produced by the data of the critical study.
Common POD values are NOAELs or lowest observed adverse effect level (LOAELs). NOAELs represent
a threshold dose administered in the critical study below which no adverse effects occurred. The LOAEL
is the lowest dose administered during the critical study where an adverse effect occurred. Because
NOAELs are the more protective values, they are generally preferred when calculating the RfD or RfC. In
situations where a LOAEL is used to calculate the RfD or RfC, an additional UF of 10 is applied to the RfD
calculation. As discussed earlier, additional UFs, usually in multiples of 10 are applied for interspecies
extrapolation when using data from animal critical studies, and for extrapolating data from acute or sub-
chronic studies to evaluate chronic effects. An additional UF of 10 is also typically applied to account for
inter-individual differences in susceptibility so that the most sensitive populations are protected. The final
RfD is therefore expressed as the quotient of the NOAEL or LOAEL/composite UF [combined product of
all UFs and modification factors (MFs)]. The RfD represents a non-linear dose threshold below which
effects are not expected to occur or are extremely unlikely in an exposed population (NRC, 2009). The
concept of a threshold dose is based on the idea that homeostatic and cellular repair mechanisms in the body
prevent toxic end points from occurring at doses below the threshold (NRC, 2009).

The dose-response assessment for carcinogens differs slightly from non-carcinogens. If a weight of
evidence evaluation indicates that an agent is carcinogenic or likely carcinogenic to humans, dose-response
data are evaluated using an epidemiological or experimental animal study. Once an appropriate study has
been identified, dose-response data from the study are evaluated in a two-step process (EPA, 2005). The
first step is similar to evaluating non-carcinogens, where a non-linear POD is identified in the lower end
of the dose-response curve that is produced by the study. The second step involves using low dose extrapolation
models to extrapolate the non-linear, and high doses from the study to linear data associated low chronic
doses that are typically associated with cancer development in human receptors to obtain a linear dose-
response curve from which a cancer slope factor is calculated. This second step in the dose-response
assessment is due to the non-threshold nature associated with cancer development resulting from exposure
to carcinogens. Because cancer is the culmination of a series of mutations triggered by low levels of chronic
exposure to carcinogens, it is assumed that there is not a threshold, a dose below which adverse effects are
not expected to occur (NRC, 2009).

The POD marks the starting point for low dose extrapolations (EPA, 2005) (Refer to Figure 2.1). There are
a number of low-dose extrapolation models available which fall into two categories: toxicodynamic
(biologically-based modeling) or empirical (measurement-based statistical modeling) (EPA, 2005). If dose-
response data are being obtained from animal studies, doses from the study must be scaled to human
equivalent doses prior to applying a low dose extrapolation model to the data. A common scaling technique
that is applied is using mg/kg \(^{1/3}\) per day (milligrams of the agent normalized by the \(1/3\) power of body weight
per day) (EPA, 2005). Following low dose extrapolation, the 95\(^{th}\) percent confidence limit of the slope of
the dose-response curve produced by the extrapolation is calculated (Hodgson, 2010). This value, referred
to as the cancer slope factor, represents the probability of cancer development associated with a particular exposure level. When evaluating a toxicant during a risk assessment, exposure levels that exceed a $1 \times 10^{-6}$ probability of cancer (i.e., ‘one in a million’) are typically considered an unacceptable risk.

Figure 2.1 – Dose-response depicting the CSF and linear extrapolation. Obtained from the U.S. Environmental Protection Agency. [https://toxtutor.nlm.nih.gov/06-003.html](https://toxtutor.nlm.nih.gov/06-003.html). Accessed 5/12/18.

The current methods used in a dose-response assessment rely heavily on data obtained from controlled animal, controlled human clinical, or epidemiological studies. Until recently, utilizing these studies to obtain toxicity data has been the cornerstone of modern toxicity testing. However, data produced by these methods are accompanied with high levels of uncertainty. This uncertainty is due to the need to make inferences and risk estimates with regard to populations, and exposure scenarios that are well beyond the conditions and parameters in which the study was conducted. Thus, the data produced during a dose-response assessment tend to exhibit varying levels of uncertainty with regard to two categories: species and dose extrapolations and inter individual heterogeneity. For species and dose extrapolation, the current methods rely mainly on statistical low dose extrapolations and species body weight scaling to reconcile differences in exposure levels when evaluating a carcinogen. When a non-cancer end point is being evaluated, an even more simplistic approach is taken by adding an UF to account for dose extrapolations, and/or species scaling. Neither of these approaches accurately capture the differences in biological responses that may occur between low chronic doses, and high acute doses, and between laboratory animals and human receptors. Effects that occur at high doses may result from metabolic processes that do not occur at lower doses. In contrast, high doses may cause toxic responses that prevent the detection of biological interactions between the chemical and signaling pathways that cause subtle but important adverse effects (NRC, 2007). In recent years increased observations of previously undetected adverse effects at low exposure levels have even led to uncertainty regarding the threshold approach currently used to evaluate non-carcinogens. For example, even low doses of toxicants are capable of occupying cellular receptor sites, therefore inhibiting the binding of ligands that would normally occupy the receptor. Under normal conditions, the binding of these cellular receptors by specific ligands results in the activation of a specific cellular response pathway such as gene expression. Therefore, the occupation of these receptor sites by toxicants even at low doses, can prevent the receptor from activating necessary cellular responses such as gene expression or cellular transduction (NRC, 2009). Furthermore, exposure to low doses of groups of toxicants such as organochlorines may predispose the cell to other toxicants that bind to cellular receptors.
(NRC, 2009). In addition, subtle adverse effects with no apparent thresholds including IQ and neurobehavioral effects have been observed at very low exposure levels for toxicants such as lead and methylmercury (NRC, 2009). For scaling the doses administered to laboratory animals to human receptors, the scaling methods typically rely on body weight adjustments, rather than addressing the physiological differences in how the two species may respond to a particular toxicant. Even though the fundamental biology of laboratory animals is generally similar to humans, there are several examples of toxicants that elicit different responses in laboratory animals and humans due to the presence of different metabolic enzymes that may activate or deactivate a toxicant. For example, rats (a common laboratory animal) are not susceptible to the toxicant thalidomide even though human fetuses are sensitive to it (NRC, 2007). With respect to human heterogeneity, the current dose-response methods do a poor job capturing inter-individual differences that may make a receptor more or less susceptible to a particular toxicant at different exposure levels. These susceptibility factors such as age, genetics, pre-existing conditions, or concurrent or former exposure to additional toxicants can drastically lower the exposure level at which a particular receptor is vulnerable (NRC, 2009). Although most risk assessments currently make an effort to protect the most sensitive sub-populations during the dose-response assessment, that effort is typically manifested by the addition of an UF, rather than a true characterization of the variation in susceptibility factors amongst potential receptors. Fortunately, developments in in vitro testing and genetics are leading to new methods in toxicity testing that will allow researchers to examine gene expression following exposure and gain increased knowledge of at risk genotypes for particular toxicants.

2.2. Exposure Assessment

Following the toxicity assessment phase of the risk assessment, the next step, exposure assessment, involves characterizing the potential exposure of receptors to the particular toxicant of concern. During the exposure assessment, a variety of measurement and modeling techniques are used to estimate the exposure concentration, potential dose, applied dose, internal dose, and target dose that is received by receptors that are exposed to the toxicant under investigation. Exposure is the product of both the toxicant concentration within an environmental media (exposure concentration) and receptor exposure factors. Therefore, to estimate the potential dose of a receptor (i.e. the concentration of toxicant that enters the body prior to being absorbed) data associated with the concentrations of particular toxicants in environmental media are combined with exposure factor data associated with a particular receptor (individual or population). (Refer to equation 1.2).

Depending on the goals of the risk assessment, three methods are commonly used during exposure assessment: direct measurement of exposure at point of contact, estimates of exposure through scenario evaluation, and exposure estimation by reconstructing internal dose (EPA, 1992). During point of contact direct measurement, devices are used to measure the concentration of the toxicant directly at the interface of the environmental media and the receptor (EPA, 1992). A classic example of point of contact direct measurement is the use of radiation dosimeter badges worn by workers exposed to gamma radiation. The dosimeter badges provide an accurate measurement of gamma radiation exposure for the time period that the badge was worn. This data can then be used in various exposure models and equations to estimate the receptors exposure over a defined time period. Alternately, dosimeters, and similar devices can be worn during specific activities where exposure to harmful concentrations of a particular chemical may occur, such as occupational activities. Exposure results are then compared to an activity specific risk threshold such as maximum radiation exposure per/year, or maximum exposure allowed without respiratory protection. Although direct point of contact measuring provides the most accurate measurement of exposure and potential dose, historically the method has been limited by the associated cost for direct measurement devices. However, as will be discussed in subsequent sections, advances in monitoring technology are
creating the potential for point of contact measurement to be made a much finer spatial and temporal scale using low cost instrumentation.

The most commonly used risk assessment method when evaluating non-occupational exposure to environmental contaminants is estimates of exposure through scenario evaluation. This method typically involves using environmental sampling and/or fate or transport modeling to determine the environmental media the toxicant will be found in so that the routes of potential exposure (ingestion, inhalation, or dermal contact) can be determined. After identifying the exposure route(s) of concern, the exposure concentration of the toxicant in the environmental media is determined through direct sampling, or evaluation of previous sampling data. The next step involves linking the exposure concentration to exposure factor data obtained from direct measurements, census information, questionnaires, or additional references such as EPA’s Exposure Factors Handbook, to determine values for the exposure factors that will be used to calculate dose. The EPA Exposure Factor Handbook provides a summary of the available statistical data on various exposure factors including drinking water consumption, soil ingestion, inhalation rates, dermal factors including skin area and soil adherence factors, consumption of fruits and vegetables, fish, meats, dairy products, homegrown foods, human milk intake, human activity factors, consumer product use, and building characteristics (EPA, 2011). The data in the Exposure Factor Handbook is obtained from a variety of different studies in the scientific literature, and other publicly available sources (EPA, 2011). A full list of all the data sources used for the Exposure Factor Handbook is beyond the scope of this paper, but in broad terms, the EPA targets studies that focus on the general population (e.g., Center for Disease Control and Prevention [CDC] and the National Health and Nutrition Examination Survey [NHANES]), or a sample population from a specific area or group (e.g., fish consumption among Native American children) (EPA, 2011). The final step is calculating intake doses for each exposure route of concern (see Equation 1.2).

The third method that is used during exposure assessment is estimating exposure by reconstructing the internal dose. During this method, biomarkers such as toxicant or metabolite concentrations in urine, blood, and tissue samples are measured after exposure, intake and uptake have occurred. These measurements can be used to back calculate dose. This method is different than the previous two, in that it has the potential to determine if absorption and therefore toxic action of a toxicant has occurred. However, caution must be exercised when evaluating the metabolite concentrations in biological media. In many instances, the presence of metabolites is not necessarily the result of exposure to the parent compound, but rather the result of exposure to the metabolite. In addition, there is individual variability in metabolic capabilities for detoxification (i.e., genetic polymorphisms) Currently dose reconstruction methodologies are only available for a limited number of toxicants, however, as discussed in Section 4, an increase in large sets biomonitoring data may increase the number of toxicants for which dose reconstruction can be performed (EPA, 1992).

Currently, the methods used in exposure assessment, particularly generating estimates of exposure through scenario evaluation produce data that are associated with varying degrees of uncertainty. Data uncertainty in the Exposure Assessment can be divided into scenario uncertainty and parameter uncertainty (EPA, 1992). Scenario uncertainty describes the inability of the exposure assessment to accurately characterize a particular exposure scenario due to inadequate environmental or incomplete exposure information. Parameter uncertainty refers to uncertainty generated from the data obtained for the various steps of the exposure assessment. Such data may include environmental data or human exposure factor data. Examples of environmental data include, but are not limited to sampling data, monitoring data, or the data related to the presence of other environmental stressors in environmental media. Data related to human exposure factors include, inter- and intra-individual receptor data such as age, gender, time – activity patterns, and diet. Parameter uncertainty also includes uncertainty created by using surrogate values for variables related
to both environmental parameters and human exposure factors. In addition to parameter and scenario uncertainty, the inability of the exposure assessment to adequately characterize the heterogeneity and variability that will exist for environmental and human exposure factors also contributes to uncertainty. This variability may include spatial and temporal differences in environmental toxicants, as well as inter- and intra-individual exposure factors. It is noteworthy to mention that the presence of variability in exposure data is not by itself considered uncertainty, because it is expected that high levels of both environmental and receptor variability will exist in any exposure scenario. However, the inability of an exposure assessment to accurately capture the variability in an exposure scenario can create uncertainty in the accuracy of the exposure assessment results. Despite the increased of more advanced statistical models in exposure assessment including Monte Carlo analysis, uncertainty still plays a major role in exposure assessment due to the inability of the current methods to generate robust and accurate data in regards to environmental conditions and exposure factors that that influence the exposure scenario.

Figure 2.2 illustrates uncertainties that are associated with the current Risk Assessment process. There are uncertainties in the Toxicity Assessment where the Hazard Identification and Dose-response Assessment steps generate RfD, RfC, and CSF values that are typically based on data obtained from acute or sub-chronic animal studies. There are uncertainties associated with the Exposure Assessment where limitations in both environmental and exposure factor data produce exposure estimates with high levels of uncertainty. Combining the uncertainties described in both the toxicity assessment and the exposure assessment, produces an overall risk characterization that compares an intake dose based on exposure data that are not uniquely representative to the exposure setting to toxicity thresholds \(i.e.\) RfD or RfC that are generated from extrapolations across species, doses and routes. Herein lies the uncertainty presented by the current risk assessment process. The uncertainty that is generated by the methods currently used has the potential to produce risk assessment results that do not accurately and efficiently characterize the risk. This mischaracterization can result in over- or under-estimation of risk (which each come with their own challenges). Furthermore, the current methods are limited in their ability to quickly adapt to future changes in that exposure scenario. Sections 3 and 4 of this paper will identify several emerging techniques and strategies that may potentially reduce or eliminate the uncertainties and limitations of the current risk assessment methods.
Figure 2.2 - Summary of uncertainties (shown in black boxes) associated with data generated from common methods currently used in the risk assessment process.
3. Emerging Techniques and Strategies for Toxicity Assessment

3.1. Paradigm Shift toward Toxicity Pathway Testing

The sections below describe a variety of new technologies and methods in various stages of development that will potentially lead to a more efficient and accurate toxicity assessment. Although the application, and required expertise differ for each method and technology, they are linked by a common goal of moving the toxicity assessment away from obtaining toxicity values using laboratory animals and toward evaluating and identifying toxic end points using human cells and tissues with more relevant exposure doses and durations (and less animal sacrifice). To achieve this goal, researchers have focused on developing methods that identify toxicity pathways at the cellular level, and subsequent adverse outcome pathways (AOPs) at the tissue and organ level. Toxicity pathways can be defined as cellular response pathways that, when sufficiently perturbed in an intact animal, are expected to result in adverse health effects (NRC, 2007). A perturbation of a toxicity pathway can potentially lead to an AOP, which describes the sequential chain of causal events at different biological levels that lead to an adverse response such as a toxic end point (EPA, 2014). Figure 3.1 demonstrates that when a cell is initially exposed to an environmental toxicant it activates a variety of cellular response pathways to maintain normal cellular function. (EPA, 2014). However, when toxicants are applied in increasingly high concentrations, and/or for a longer duration in combination with other stressors, in sensitive hosts, or sensitive life stages, cellular defense pathways can fail. Failure of these response pathways results in perturbation of toxicity pathways producing cytotoxic outcomes including, but not limited to changes in differentiation and proliferation, apoptosis, necrosis, and formation of DNA adducts. Continued exposure will result in continued cytotoxicity at the cellular level and eventually result in toxic end points that are detected at higher levels of biological organization such as tissues and organs. (Refer to Figure 3.2 in the Appendix for a simplified toxicity pathway perturbation with liver cancer as a toxic end point). The toxic end points observed at these higher levels of biological organization currently serve as the end points used in the majority of toxicity studies. By replacing this traditional method of observing toxic end points at the tissue and organ level with identifying the precursor cellular toxicity pathway perturbations, researchers will be able to detect responses to environmental toxicants at the beginning stages of their biological effects. This earlier detection will allow for the evaluation of toxic effects at exposure doses that are significantly smaller and more relevant to human exposure doses. This includes the evaluation of linear non-threshold effects that are currently not evaluated for non-cancer end points and evaluated via extrapolation for cancer end points. Further accuracy will be obtained if identification and evaluation of perturbations in toxicity pathways can be obtain using human cells. Fortunately, during the last decade, there have been several advances and developments in toxicity testing, computational modeling, molecular biology, and genetics that demonstrate a potential future where toxicity assessments are performed by evaluating human responses at relevant doses that even account for variation in genetic susceptibility factors. The sections that follow, will identify and discuss several of these methods.
Figure 3.1 - Simplified flow chart depicting the potential toxic effect following exposure to an environmental toxicant, and the detection differences in current vs future methods of toxicity assessment. As the dose concentration or duration increases (depicted by the arrow to the left of the Dose Concentration/Duration), cellular defense pathways can fail resulting in perturbation of toxicity pathways producing cytotoxic endpoints. Continued increase in dose and/or duration will eventually result in tissue damage, which currently serves as the toxic end point for most toxicity assessments.

### 3.1.1. Hazard Identification

Section 2 described the uncertainties and limitations of the current methods that are used during hazard identification. The current methods used during hazard identification rely on identifying adverse effects associated with human exposure to a particular toxicant using controlled human clinical, epidemiological, and controlled animal laboratory studies. Of these three options, controlled animal laboratory studies are used the most frequently. Therefore, much of the current uncertainty associated with hazard identification is related to using data associated with acute doses administered to laboratory animals to identify toxic end points for human populations typically exposed to lower and more chronic doses. Using the concept of cellular toxicity pathways and AOPs, developments in toxicity testing, computational modeling, molecular biology, and genetics have introduced new methods to replace the current hazard identification process. Particular methods that demonstrate potential use for future hazard identification include: high throughput screening (HTS) in-vitro toxicity testing, development of quantitative structure–activity relationship (QSARs) and toxicity pathway models and use of genetic biomarkers.

3.1.1.1. High Throughput Screening In-Vitro Toxicity Testing

HTS in vitro assays are efficiently designed in vitro bio assays that can be automated to rapidly measure the effects of environmental toxicants on a biologic process of interest, preferably using human cell lines. These assays evaluate hundreds to thousands of chemicals over a wide concentration range to identify chemical actions on gene, pathway, and cell function. The development of in vitro HTS assays can be attributed to significant advancements in molecular biology that has elucidated mechanisms in which environmental toxicants can perturb toxicity pathways. This increased understanding in toxicity pathway perturbation has prompted the development of hundreds of in vitro HTS assays capable of testing a variety
of toxicity pathways. Perhaps the most notable of these developments has been the EPA’s ToxCast program which is part of the Tox21 program, a collaboration between the EPA, National Institute of Health (NIH), including National Center for Advancing Translational Sciences and the National Toxicology Program at the National Institute of Environmental Health Sciences, and the Food and Drug Administration (FDA). The goal of the Tox21 program is to develop methods to quickly and efficiently test the potential of toxicants to disrupt processes in the human body that may lead to negative health effects (Judson et al., 2014). Under the ToxCast program, EPA has tested over 1,800 chemicals using 700 different types of high throughput assays covering a range of cellular responses, and approximately 300 signaling pathways (Judson et al., 2014). Furthermore, data generated from the assays are published on EPA’s ToxCast Dashboard where it is available to the public.

There are several advantages to utilizing HTS in vitro assays for hazard identification over the current methods: (1). In vitro HTS allows scientists to evaluate the perturbations to cellular toxicity pathways using human cell linings. Significantly reducing the limitations that are associated with data generated from laboratory animal studies, and finally allowing scientists to evaluate toxic end points associated with more relevant doses; (2). In-vitro HTS assays are capable of quickly and efficiently evaluating multiple cellular responses of chemicals over a range of doses, allowing scientist to confirm and refine knowledge related to well-studied toxicity pathways, identify new toxicity pathways that may have not been discovered using traditional toxicity testing, and identify chemicals that act through similar pathways; (3). In vitro HTS is both faster and significantly less expensive than traditional toxicity testing, which will allow for screening of thousands of chemicals for which there is currently limited or no available toxicity data; (4). Data obtained from in-vitro HTS can be combined with other technologies and methods such as genetic biomarkers, and QSAR modeling to further enhance the accuracy and level of detail of the toxicity assessment.

The use of in vitro HTS to screen chemicals with limited toxicity data was demonstrated by the EPA Office of Research and Development by evaluating the cytotoxicity of eight oil spill dispersants being used or being considered for use during cleanup of the Deep Water Horizon Spill in the Gulf of Mexico. Some dispersants contain nonylphenol ethoxylates (NPEs), which can degrade to nonylphenol (NP), a known endocrine disruptor. Thus, eight of the 16 assays performed focused on estrogen and androgen receptor activity. Tests were performed across a wide range of concentrations (0.001 ppm – 10,000 ppm). Results revealed that none of the eight dispersants displayed significant endocrine activity through the androgen or estrogen signaling pathways at biologically relevant doses. (EPA, 2010). This study demonstrated the potential of in vitro HTS in situations where chemicals with limited toxicity data need to be evaluated quickly.

The use of in-vitro HTS to refine current knowledge related to toxicity pathways and identify new information regarding toxicity pathways was demonstrated by Hsieh et al. (2017) in a study that demonstrated that there may be a link between the kinetics of cytotoxicity and the corresponding toxicity pathway perturbation responsible for cytotoxicity. In this study, the cytotoxicity of approximately 10,000 chemicals were evaluated at 0, 8, 16, 24, 32, and 40 hours of exposure in a concentration dependent fashion in human embryonic kidney cell lines, and human hepatocellular carcinoma cell lines (Hsieh et al., 2017). Cytotoxicity was evaluated using two different assays: one measuring the metabolic activity of cells (i.e., cell viability, glo) while the other evaluates cell membrane integrity (i.e., cell death, flor). (Hsieh et al., 2017). Chemicals were grouped by cytotoxicity kinetics (i.e. the earliest time interval where maximum cytotoxic effects occurred). These groups were then further evaluated based on toxicity pathways using the Tox21 nuclear receptor and stress response pathway assays to determine if a relationship existed between cytotoxicity kinetics and the effected toxicity pathway. Results revealed that pathways such as the activation
of the histone H2AX, which is associated with DNA repair, corresponded to faster cytotoxicity kinetics while activation of the transcription factor TP53 was associated with slower cytotoxicity kinetics. Associations between the nuclear receptor Nrf2 and androgen receptor pathways based on similar cytotoxicity kinetics were also identified, and subclass of androgen receptor antagonists that also cause cytotoxicity via oxidative stress associated with Nrf2 activation was suggested (Hsieh et al., 2017). This study demonstrates that relationships may exist between the cytotoxic kinetics and the corresponding toxicity pathway perturbations. Such relationships may assist researchers in identifying the possible toxicity mechanisms of environmental toxicants based on their cytotoxicity kinetics, which will allow them to prioritize which toxicity pathway assays should be evaluated for a particular environmental toxicant. (Refer to figure 3.3 in the Appendix for a summary of the association between cytotoxicity kinetics and toxicity pathways that were evaluated in this study). Results from this study also demonstrate how chemicals may be grouped based on the particular toxicity pathways that they affect. The creation of such groups may provide a mechanism by which chemical mixtures can be evaluated. Chemical combinations that interact with the same toxicity pathways could be tested over a broad range of doses to evaluate potential synergistic relationships. The data generated from assays could allow for an intelligent and focused approach to the problem of assessing exposure to mixtures (NRC, 2007).

To demonstrate how HTS data could be combined with genetic biomarkers, to further enhance the accuracy and level of detail of the toxicity assessment, Abdo et al. (2017) demonstrated that in vitro HTS can be used to rapidly assess the magnitude and genetic causes of inter individual variability in genetic susceptibility factors (toxicodynamic). HTS (CellTiter Glo –Luminescent Cell Viability Assay) techniques were used to assess cytotoxicity of 179 different chemicals at 8 different concentrations in 1,086 lymphoblastoid cells (LCLs) spanning 9 populations from five continents (Abdo et al., 2017). The LCLs were obtained from the 1,000-genome project. Cytotoxicity was measured as effective concentration, 10th percentile (EC10). Genotype analyses was performed to identify single nucleotide polymorphisms (SNPs) and other genetic influences on the variability factors (Abdo et al., 2017). Results indicated that for approximately half the tested chemicals, cytotoxic responses in 1% of the most sensitive individuals occurred at concentrations within a factor of 10^{1/2} (i.e. the factor typically used in traditional toxicity assessment) of the median individual (Abdo et al., 2017). However, for many compounds the variability factor was greater than 10. Genetic analysis suggested that SNPs in genes encoding for membrane and transmembrane solute carrier had a strong influence on variability factors (Abdo et al., 2017). This study demonstrates how data from HTS in vitro assays can be used to assess inter individual variability in genetic susceptibility factors, which is a limitation in current risk assessment. Additional uses of genetics in toxicity assessment will be discussed in the next section.

3.1.1.2. Genetic Biomarkers
As described in the previous section, a common feature in many toxicity pathway perturbations is alteration in the expression of particular genes. This change in expression is typically related to changes in transcription factors related to stress response, or cell signaling such as endocrine receptors, and nuclear receptors. While in vitro HTS assays provide a method to evaluate pathways involved in alterations of gene expression, additional studies have demonstrated the potential for evaluating changes in gene expression using biomarkers from actual human populations where initial exposure concentrations are known. A series of such studies by Thomas et al. (2014) and McHale et al. (2010) examined the use of biomarkers in benzene induced hematoxicity. McHale et al. used microarray analysis to analyze gene expression in the peripheral blood mononuclear cells of 125 workers exposed to benzene at concentrations ranging from < 1 ppm to > 10 ppm (McHale et al., 2010). Results identified alterations in 147 genes that were related to benzene exposure. Of the 147 genes, 16 genes associated with immune response, inflammatory response, cell adhesion, cell matrix adhesion, and blood coagulation were significantly altered at all exposure levels
including those below the current U.S. Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) of 1 ppm (McHale et al., 2010). Furthermore, these 16 genes were strongly associated with acute myeloid leukemia (AML). This 16 gene signature may therefore be used as a future biomarker for leukemia in benzene exposed populations (McHale et al., 2010). Similar results were observed in a subsequent study conducted by Thomas et al. (2014) where RNA sequencing was used to evaluate benzene induced hematoxicity (EPA, 2014). The results of both studies demonstrate how genetic biomarkers could serve as a valuable tool in risk assessment, specifically when evaluating a smaller group of receptors where obtaining biological samples for genetic analysis may be feasible. Genetic biomarkers could also play a role in developing HTS assays for environmental toxicants by identifying relevant pathways and doses to test.

3.1.1.3. Computational Methods: QSARs and Toxicity Pathway Modeling

A variety of new QSAR models exist to predict how an environmental toxicant’s physical and chemical properties will influence its stability in the environment, potential for exposure, route of exposure, bioaccumulation potential, routes of metabolism, toxicity and metabolite toxicity. Such models include, but are not limited to, models that predict tissue solubility and protein binding such as CASE/MULTICASE and TOPKAT, and rule-based models such as DEREK and ONCOLOGIC (NRC, 2007). Since QSAR models base model predictions on a template chemical structure, the availability of a variety of such structures has historically been a limiting factor in the development of QSAR models. However, with the development of in vitro HTS, and the robust databases that are generated, there is the potential for a surge in available template chemicals, and therefore the development of subsequent models. This potential was demonstrated in the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP). The CERAPP is a large-scale modeling project comprised of 40 categorical and 8 continuous models that used various QSAR techniques to screen 32,646 chemical structures for estrogen receptor (ER) related activity for prioritization for further testing (Mansouri et al., 2016). Models were developed in collaboration with 17 groups in the U.S. and Europe and were trained using HTS of 1,667 chemical structures obtained from EPA ToxCast. Models scored each of the 32,646 chemical structures based on ER agonist, antagonist and binding activity. Each chemical was assigned a score in between 0 and 1 based on the ER agonist, antagonist or binding activity level of each chemical with a score of 0 representing inactive agonist, antagonist or binding activity and a score to 1 representing strongly active agonist, antagonist or binding activity. The prediction accuracy of each model was evaluated on the ER activity of a set of 7,522 chemicals which were obtained from the literature. (Mansouri et al., 2016). Results of the CERAPP revealed that individual model scores ranged from 0.69 to 0.85, and showed high prediction reliabilities (Mansouri et al., 2016). A consensus model was developed based on the accuracies of each individual model. Out of the 32,464 chemicals, the consensus model predicted 4,001 chemicals (12.3%) as high priority actives and 6,742 potential actives (20.8%) to be considered for further testing (Mansouri et al., 2016). The CERAPP demonstrated the possibility of using the robust data from ToxCast to develop a consensus model capable of screening large libraries of chemicals.

A novel concept that combines the principles of QSAR models with toxicity pathway characterization is the development of toxicity pathway models. These models interpret toxicity pathways in a mechanistic step-wise manner by identifying rate limiting and signaling nodes (NRC, 2007). An example of a toxicity pathway for which a toxicity pathway model may be developed is the Nrf2 activation pathway. Nrf2 is a transcriptional regulator which in toxic environments, activates the transcription of antioxidant genes. This activation occurs when oxidants interact with the cytoplasmic protein Keap-1, which is normally bound to Nrf2 in non-toxic environments. The interaction between oxidants and Keap-1 inactivates Keap-1, causing Nrf2 to be released and translocated to the nucleus where it heterodimerizes with the protein Maf and binds
to antioxidant response elements resulting in the expression of antioxidant response-stress proteins and phase 2-detoxifying enzymes (refer to Figure 3.4). Motohashi and Yamamoto (2004) suggested that two parts of the Nrf2 toxicity signaling pathway could be modeled to predict low dose toxic responses: the inactivation of Keap-1 by oxidants and subsequent formation of the NrF2-Maf heterodimer, and the expression of antioxidant response-stress proteins and phase 2-detoxifying enzymes (Motohashi and Yamamoto, 2004). In addition to the Nrf2 activation pathway, additional models have been developed for toxicity pathways related to heat shock response and nuclear factor kappa-B mediated inflammatory signaling in response to cytokine (NRC, 2007).

Figure 3.4 – Description of the Nrf2 activation pathway. Obtained from Motohashi and Yamamoto (2004).
3.1.2. Dose-response Assessment

The methods described in the previous section center around identifying toxic end points on the level of cellular toxicity pathway perturbations. In particular, most future methods seem to rely heavily on data obtained from in-vitro assays. However, the data generated from these assays is limited unless it can be accurately extrapolated from the in vitro cellular level to the in vivo organism level. To accomplish this task, a dose-response approach is being developed that is tailored to such an extrapolation. This future dose-response will rely heavily on modeling human absorption, distribution, metabolism, and elimination (ADME) of environmental toxicants. This approach will rely heavily on physiologically based pharmacokinetic (PBPK) reverse dosimetry modeling. In addition, the development of virtual tissues (VTs) and organs will allow researchers to evaluate and interrupt the effects of doses associated with in vitro toxicity pathway perturbations on multiple levels of biological organization to ensure that the most sensitive AOPs are being evaluated. (EPA, 2014). Although each of these extrapolation methods come with a certain degree of uncertainty, they represent a significant step forward in regards to the accuracy compared to the current dose-response methods. The current dose-response methods use a blanket UF to account for extrapolation between species and between acute and chronic doses. Unlike the current dose-response methods, the methods described here will potentially be able to extrapolate from in-vitro doses associated with chronic end points in human cells to exposure doses that use mathematical models to account for the specific ADME properties of a particular environmental toxicants.

3.1.2.1. PBPK Based Reverse Dosimetry Modeling

A PBPK model uses mathematical equations to model the ADME characteristics of a toxicant in an organism [refer to Figure 3.5 (Louisse et al., 2017)]. PBPK models require information for three parameters: physiological and anatomical parameters (e.g. cardiac output, tissue volumes, and tissue blood flows), physiochemical parameters of the toxicant of interest, and kinetic parameters (e.g. kinetic constants for metabolic reactions) (Louisse et al., 2017). Values for physiological and anatomical parameters are usually obtained through literature, physiochemical parameters can be obtained experimentally, and kinetic parameters can be obtained using in vivo kinetic values, in vitro methods such as incubations with liver enzymes, or prediction via in silico methods (Louisse et al., 2017). PBPK models have been traditionally used to derive a tissue doses from exposure or internal dose. However, PBPK-based reverse dosimetry, operates in the reverse order where an internal or exposure dose is obtained from an in vitro concentration. Alternatively, PBPK-based reverse dosimetry can be used to obtain an exposure dose from human biomonitoring data (this concept is further explored in section 3.2).

First proofs of principle PBPK-based reverse dosimetry models have been developed for neurotoxicity, developmental toxicity, nephrotoxicity, hepatotoxicity, DNA adduct formation, and nuclear receptor activation/inhibition. DeJongh et al. (1999) used PBPK-based reverse dosimetry modeling for the rat to predict the neuro toxicity of benzene, toluene, lindane, acrylamide, paraxoxon, caffeine, diazepam, and phenytoin from EC$_{20}$ values obtained from in vitro studies with human neuroblastoma cells. (Louisse et al., 2017). The model predicted toxicity values were compared to LOAEL values for rats from the literature, and differences between the two values range from 2 to 10-fold (Louisse et al., 2017). A similar study was conducted by Forsby and Blaabjerg (2007) where the lowest observed effective dose (LOED) associated with neurotoxicity was determined for acrylamide, lindane, parathion, paraxoxon, phenytoin, diazepam and caffeine using in vitro toxicity data and subsequent PBPK based reverse dosimetry modeling. Voltage operated Ca$^{2+}$ channel (VOCC) function, acetylcholine receptor function and neurite degeneration were evaluated to determine the neuro-specific endpoints excitability, cholinergic signal transduction and axonopathy, respectively (Forsby and Blaabjerg, 2007). In addition, cellular protein levels following exposure were used for general cytotoxic endpoints (Forsby and Blaabjerg, 2007). The lowest concentration
that induced 20% effect (EC$_{20}$) was determined for each toxicant and each endpoint respectively (Forsby and Blaaboer, 2007). The lowest EC$_{20}$ values were then integrated along with ADME data into a PBPK based reverse dosimetry modeling for the rat, from which LOED values were obtained. The LOED value was used to represent the exposure concentration associated with each particular EC$_{20}$ value, which the researchers used to represent respective tissue doses (Forsby and Blaaboer, 2007). Results of the study revealed that there was a good correlation (within one order of magnitude) between the estimated LOED values and experimental LOED values obtained from the literature (Forsby and Blaaboer, 2007). Furthermore, the study demonstrated evidence that impaired VOCC function maybe a mechanism responsible impaired learning caused by sub chronic exposure to lindane (Forsby and Blaaboer, 2007). This finding is significant, because the current mechanism for impaired learning following sub chronic exposure to lindane is currently unknown (Forsby and Blaaboer, 2007). An example of PBPK-based reverse dosimetry modeling for developmental toxicity was demonstrated by Verwei et al. (2006) who developed a PBPK-based reverse dosimetry model for in vitro EC$_{50}$ values from an ES-D3 cell differentiation assay (Louisse et al., 2017). Predicted dose levels were compared to literature values. Comparisons of the two sets of values revealed that in vivo effect levels for ethylene glycol monomethyl ether (EGME), ethylene glycol monoethyl ether (EGEE), methotrexate, and retinoic acid were correctly predicted but that the in vivo effect level for 5-fluorouracil was overestimated (Louisse et al., 2017). The authors of this study concluded that PBPK-based reverse dosimetry modeling appeared to be a promising alternative for risk assessment of embryo toxic compounds (Louisse et al., 2017). Abdullah et al. (2016) used PBPK reverse dosimetry modeling to predict nephrotoxicity associated with exposure to aristolochic acids using in vitro toxicity data from porcine and canine kidney cells (Louisse et al., 2017). Bench Mark Dose lower limit of the 95% confidence interval (BMDL$_{10}$) values were derived from the PBPK based reverse dosimetry model and compared to POD from the literature (Louisse et al., 2017). Comparisons of the two sets of values revealed that values predicted by the model were generally within the same order of magnitude as values obtained from the literature (Louisse et al., 2017).

It is noteworthy to mention that the proofs of principle studies, including those discussed in this section have only been validated using dose-response data from controlled laboratory animal studies. For this reason, the majority of the proof of principle studies have used laboratory animal PBPK based reverse dosimetry. Therefore, future challenges in the development and use of PBPK based reverse dosimetry will include developing a PBPK based reverse dosimetry model that can be validated using human dose-response data. It can be expected that the first part of this challenge (i.e. developing a human PBPK based reverse dosimetry model) should be met by using in vitro toxicokinetic data and computational modeling. However, as discussed in Section 2, experimental human dose-response data is limited. Therefore, validating human PBPK based reverse dosimetry models with experimental human dose-response data may remain a challenge.
3.1.2.2. Virtual Tissues

Perhaps the most advanced in vitro to in vivo extrapolation technology currently in development are VTs. VTs are computational models that predict histopathological alterations and AOPs from doses associated with perturbations of cellular toxicity pathways (Shah and Wambaugh, 2010). These models use information regarding the structure of the altered biological pathways and explicitly address and represent the spatial and temporal dynamics of multiple levels of biological organization (EPA, 2014). Many of these models use agent-based modeling (ABM) where cells are represented by agents. These agents mimic cellular interactions, and cellular responses to the microenvironment (ME), including perturbations to toxicity pathways (Shah and Wambaugh, 2010). The behaviors of each agent are constrained by physical laws and mechanistic rules which are derived from experimental evidence. VTs currently in development include:

1. European Virtual Physiological Human project (Hunter et al., 2010); 2. HumMod, a whole-body integrated human physiology model (Hester et al., 2011); 3. Virtual Cell (V-Cell), a spatially realistic quantitative model of intracellular dynamics (Moraru et al., 2008); 4. EPA’s Virtual Embryo™ (v-Embryo) project, a suite of models that simulate normal development leading to the formation of blood vessels, limb-buds, reproductive systems, and eye and neural differentiation (Knudsen and DeWoskin, 2011; Knudsen et al., 2011b); 5. EPA’s Virtual LiverTM (v-Liver) model that simulates the dynamic interactions in the liver, and is used to translate in vitro endpoints into predictions of low-dose chronic in vivo effects in humans (Shah and Wambaugh, 2010); 6. Virtual Liver Network (German Federal Ministry for Education and Research, 2014), a German initiative to develop a dynamic model of human liver physiology, morphology, and function integrating quantitative data from all levels of organization (Holzhutter et al., 2012); and 7. Hamner Institutes for Health Sciences’ DILIsym® project that intends to identify new molecules that might cause liver toxicity and to understand the mechanism of existing toxicants (The Hamner Institutes For Health Sciences, 2014).

Figures 3.6 and 3.7 in the Appendix depict the development and construction of a VT for the liver (Virtual Liver), and vascular tissues. The vascular endothelial VT was used to model the self-directed assembly of endothelial cells in a completed vascular network utilizing signaling response pathways involving an exchange of chemokine signaling, vascular endothelial growth factor and plasminogen activating system among several cell types. By incorporating parameters from ToxCast HTS data into this virtual tissue model.
the concentration dependent disruption of angiogenesis (formation of new blood vessels) was shown for 5HPP-33, an anti-angiogenic thalidomide analogue [refer to Figure 3.8 (Judson et al., 2014)]. Not only does this example demonstrate the potential in VT modeling, but it also demonstrates how the cell-oriented structure of the VT models are well suited for extrapolating tissue effective tissue doses from the in vitro HTS data that is generated by databases like ToxCast (Shah and Wambaugh, 2010). Although VT models are still in the early stages of development, the long-term goal of VT is to run virtual experiments that will investigate histopathological effects across chemicals (or mixtures), doses and populations (Shah and Wambaugh, 2010)
Figure 3.8 – VT model of endothelial cell organization into a complete endothelial network using CompuCell3D. Results comparing the VT model disruption for 5HPP-33 based on ToxCast data (upper panel) compared to a human angiogenesis (human umbilical vein endothelial cells– HUVEC) assay (lower panel). The middle and right panels display increasing lack of vascular organization with increasing dose. This example demonstrates how the cell-oriented structure of the VT models are well suited for the in vitro HTS data that is generated by databases like ToxCast. The use of HTS with VT may have the potential to efficiently produce accurate dose-response measurements from in vitro toxicity data. Obtained from Judson et al. (2014). Reprinted from Kleinstreuer, Dix et al. 2013.
4. Emerging Techniques and Strategies for Exposure Assessment

Section 2 summarizes the uncertainty associated with the current exposure assessment methods. The main driver for much of the current uncertainty is the inability to generate exposure concentrations which are consistently spatially and temporally representative. Current methods to determine exposure concentration rely on sampling, monitoring and modeling at a time and location which is not necessarily representative of the mobile nature of human receptors (i.e., single point or a few points in time at a limited number of locations). Exhaustive sampling that would be better representative is generally cost prohibitive. The uncertainty generated by the exposure concentration is further magnified when that value is used along with additional exposure factors to calculate potential dose. For this reason, many of the emerging technologies and strategies have focused on generating exposure concentrations with significantly finer spatial and temporal resolution which are more representative to receptor location and time compared to current methods. Emerging technologies and strategies being developed to more accurately measure exposure concentration include advances in geospatial technologies including geographical information sciences (GIS), geospatial modeling, and remote sensing, along with advances in ubiquitous chemical sensors such as nano and micro sensors. To compliment more accurate exposure concentrations, advances in location tracking technologies including geographical positioning system (GPS), Bluetooth tags, and Wifi positioning system (WPS) have the potential to determine the real time locations of receptors, and the change in exposure concentrations at each location. Use of these location tracking technologies may result in a more accurate calculation of exposure frequency and duration compared to current methods. In situations where location can still not be determined, several statistical modeling approaches have been developed to determine the likely location of a receptor. To further advance determination of receptor exposure concentration and location exposure, motion sensors such as accelerometers, and motion sensors embedded in smart phones have the potential to more accurately determine a receptor's breathing intensity for inhalation exposures. Lastly, several advances in the area of biomonitoring including, lab-on-a-chip technology and large biomarker datasets have the potential to accurately determine if exposure is causing adverse health effects, and the exposure concentration at which they occur. The replacement of current methods with the technologies and strategies discussed will potentially move the exposure assessment process from the current process which in centered around assessing discrete exposures with a focus on one exposure scenario and environmental toxicant at a time, toward an integrated approach capable of assessing exposures from source to dose on multiple spatial, temporal and biological scales.
4.1. Estimating Exposure Concentration

Emerging technologies and strategies for estimating exposure concentration fall into two broad categories: Geospatial technologies and ubiquitous chemical sensor technologies. Geospatial technologies that will be discussed include remote sensing, GIS, and geospatial modeling. Chemical sensors that will be discussed include advances in the development of both micro sensors and nano sensors. Technologies and strategies in both categories are united by the common goal of estimating exposure concentrations on a much finer spatial and temporal scale compared to current methods.

4.1.1. Geospatial Techniques

The advancements in remote sensing, GIS, and geospatial modeling have the potential to estimate exposure concentrations on a finer spatial scale with significantly less resources compared to current methods. Remote sensing can be used to estimate exposure concentrations on a large spatial scale and identify geographical anomalies that may require further attention. Geospatial modeling techniques can subsequently model exposure concentrations at finer spatial resolutions by using various interpolation techniques ranging in complexity from simple inverse distance weighted (IDW) to land use regression (LUR). GIS can then be used to combine the modeled exposure concentrations with various population, census, and land use data to identify geographical areas of concern where exposure frequency and potential risk is expected to be greatest. The use of online mapping and GIS will allow for these geospatial technologies to produce maps in near-real time which are available to the public.

4.1.1.1. Remote Sensing

Remote sensing can broadly be defined as measuring a materials electromagnetic reflectance and emission to identify and distinguish the different chemical and physical characteristics that are present on the earth’s
surface and/or in the atmosphere. The primary measurement is reflectance and emission of electromagnetic radiation from sunlight, and the primary methods of obtaining reflectance and emission data is via remote sensors present on satellites and aircraft (Figure 4.2). Six satellite sensors currently used for remote sensing include: Moderate Resolution Imaging Spectroradiometer (MODIS) which is present on two different National Aeronautics and Space Administration (NASA) satellites, Landsat, which consists of remote sensors on several satellites managed by NASA and the United States Geological Survey (USGS), commercial earth satellites including IKONOS and Orbview, Satellites Pour l’Observation de la Terre (SPOT) and Earth-observing Satellites developed by France and Sweden, and the Geospatial Operational Environmental Satellite (GOES) operated by National Oceanic and Atmospheric Administration (NOAA). Remote sensing data can be viewed directly online in several data formats including imagery (Figure 4.3 in the Appendix) and as geospacial data layers in online viewers.

Remote sensing data is capable of characterizing a variety of surface and atmospheric properties based on absorption of the unique spectral ranges (spectral indices) that are associated with molecules of different materials. Examples of spectral indices include vegetation index data such as normalized differential vegetation index (NDVI) and soil adjusted total vegetation index (SAVI), and atmospheric properties such as aerosol concentration using aerosol optical depth (AOD) data. Remote sensing data is typically presented on maps using hyper spectral and multispectral imagery where each pixel is representative of the unique spectral reflectance that occurs in that pixel. Hyperspectral imagery has the ability to detect much narrower band widths compared to multispectral imagery and can therefore identify chemical and physical properties at finer resolution.

A number of studies have demonstrated the potential of remote sensing data in exposure assessment. Li et al. (2015) used AOD data from MODIS to develop an algorithm to estimate the particulate matter less than 10 microns (PM$_{10}$) concentrations in the Pearl River Delta region of China from 2001 to 2013 in order to characterize spatial and temporal PM$_{10}$ trends in the region. The algorithm was validated by comparison to ground base data PM$_{10}$ at 98 monitoring sites from 2011 – 2013, and comparison to monthly average PM$_{10}$ concentrations at 26 monitoring sites from 2001-2013 (Li et al., 2015). Results from the 2011- 2013 data indicated that the correlation coefficient at most of the 98 stations were between 0.5-0.7, and 88 of the 98 stations had a correlation coefficient greater than 0.6. Results from 2001-2013 indicated an average correlation factor of 0.67 with areas of Hong Kong and Macao having correlation factors above 0.8 (Li et al., 2015). Figure 4.4 depicts the results of this study. These results indicate that even though there is still room for improvement, PM$_{10}$ data derived from remote sensing shows a positive correlation to PM$_{10}$ measurements that are obtained using traditional air monitoring techniques and may be an appropriate and useful tool to obtain PM$_{10}$ exposure concentrations over large geographical regions with limited air monitoring. In addition to using remote sensing techniques to determine exposure concentrations to air pollutants, studies have demonstrated its potential for determining exposure concentrations of pollutants in both water and soil. Peng et al. (2016) used remote sensing data including spectral indices for biophysical composition index (BCI), enhanced vegetation index (EVI), (LSWI), normalized NDVI, soil-adjusted total vegetation index (SATVI), soil-adjusted vegetation index (SAVI), transformed vegetation index (TVI), weighted difference vegetation index (WDVI), and tasseled cap transformation including brightness, greenness, and wetness along with additional environmental data to develop a predication model which maps the spatial distribution of heavy metals As, Cr, Pb, Cu, Ni and Zn in Qatari soils. The model used condition-based rules, which assigned different weights to each attribute, including remote sensing data, to develop a predication algorithm for each heavy metal (Details of the model will be discussed in section 4.1.1.2. However, it is noteworthy to mention that the spectral indices for NDVI, EVI and SAVI ranked in the top 10 variables for the modeling of As (Peng et al., 2016). This result indicates that remote sensing data can be highly influential in the development geospatial models for surface soil contaminants.
Additional studies using remote sensing data to predict exposure concentrations in soil include Wu et al. (2005) where hyper spectral imagery was used to study mercury contamination in suburban agricultural soils in the Nansing region of China. Use of remote sensing to predict exposure concentrations of pollutants in water include, Petus et al. (2014), who used remote sensing to effectively map the spatial and temporal variability of the total suspended matter in the Adour River turbid plume in the south-eastern Biscay Bay. In this study, Reflectance data from MODIS with a 250 m resolution was combined with a regional algorithm developed by Petus et al. (2010) to map the total suspended matter (TSM) in mg/l discharged into the south-eastern Bay of Biscay and adjacent coastal waters for 246 cloud free days (Petus et al., 2014). The Adour River turbid plume was delineated by using a 3 mg/l TSM concentration threshold and limiting the plume area to coastal areas near the Adour estuary mouth to reduce the influence of wave induced sediment resuspension in the plume maps (Petus et al., 2014). The method used in this study was able to effectively capture the seasonal and inter-annual spatial and temporal variability of the plume (Petus et al., 2014). The data generated was compared with empirical data for daily discharge rates at the Adour River mouth, daily wind direction and daily tidal information (Petus et al., 2014). Plume size, mean TSM, and max TSM were positively correlated with discharge rate, and wind direction had a substantial influence on plume location (Petus et al., 2014). In addition, a novel approach was used to characterize the spatial risk of exposure from Adour River turbid plume waters to inshore marine waters by developing frequency of occurrence maps. The value of each pixel in the frequency of occurrence map was a function of the how often that pixel was classified as having plume conditions during each of the 246 days of the study (Petus et al., 2014). The results of this study further verified the important role that remote sensing can serve when exposure predictions are required over a large spatial and temporal scale.

A common theme in the remote sensing studies identified above, is that remote sensing data must be used with appropriate algorithms and models to be used effectively in exposure assessment. This requirement is due to the fact that remote sensing data by itself can only suggest the presence of a particular material (e.g. vegetation or water) based on the presence of particular spectral indices. However, remote sensing by itself cannot estimate the concentration of a contaminant. Additional limitations include the spatial resolution of remote sensing data. However, this limitation may be temporary, as spatial resolution has increased over the last two decades as the technology has advanced. Therefore, it appears that the best use for remote sensing in exposure assessments is as a powerful component to models and algorithms that are used to predict exposure concentrations over large spatial distances, or in areas where monitoring and sampling are not feasible. In addition, AOD data may be used by itself as an exclusively visual and qualitative tool for preliminary identification of large geographical areas where exposure to aerosols may be a concern. However, any further identification of aerosol concentration in these areas would require the use of predictive models and algorithms for the remote sensing data to be useful.
Figure 4.2 – Simplistic summary illustrating the concept of remote sensing. Obtained from the Institute of Computer Systems, Odessa National Polytechnic University, Odessa, Ukraine

Figure 4.4. - Average satellite-retrieved and ground-observed PM$_{10}$ concentrations (circles) from 2011 to 2013 from a study conducted by Li et al. The figure depicts a strong correlation between PM$_{10}$ concentration predicted using remote sensing, and concentration obtained from traditional air monitoring techniques. Obtained from Li et al. (2015).
4.1.1.2. Geospatial Modeling

Geospatial modeling techniques, specifically interpolation techniques, can be used to estimate exposure concentrations at locations where measured values do not exist. The six interpolation techniques that are most commonly used are IDW, voronoi polygons, kriging, radial base functions (RBF), linear regression, and LUR. IDW, voronoi polygons, kriging, and RBF can provide quick interpolations of monitoring and sampling data. These interpolated values can be based on both deterministic methods (IDW and voronoi polygons), or geostatistical methods (kriging and radial base functions). However, in the case of all four of these methods, the interpolated value is a function the surrounding measured values (i.e. the known sample concentrations), and distance of each measured value to the interpolated value. Therefore, additional environmental variables that may influence the concentration of a particular contaminant are not considered when using IDW, voronoi polygons, kriging, or RBF. The use of either linear regression or LUR analysis, however, allows for interpolated values to be based on statistical relationships with environmental variables. In the case of linear regression, the interpolated value is based on a relationship between the measured values and one environmental variable. This method works well when there is a single environmental variable that has a significant influence on the measured values. Where linear regression is typically limited to using one environmental variable, LUR is a method that is capable of using numerous environmental variables including, but not limited to, distance to mobile or stationary sources, proximity to certain land uses, average wind speed, surface, and subsurface characteristics, and elevation. Multiple regression equations are produced comparing the sample data with each environmental variable at each sample location. The regression analyses are used to determine the relationship between each environmental variable, and the sample data at each sample location, and at defined zones of influence (buffers) around a sample location. Results of each regression analysis are combined to produce an equation which assigns weights to each environmental variable and can then be used to predict exposure concentration at unknown locations. LUR requires a considerable amount of statistical analysis, that may have traditionally limited its use. However, the combination of modern statistical software and GIS can be used to make the process much more efficient. An additional advantage to LUR is that, just like any regression analysis, an $R^2$ value is computed which indicates the power of the LUR model to explain the variability of the known sample concentration. Therefore, based on the $R^2$ value, the modeler can determine if the model is appropriate for predicting exposure concentrations before the model is even used.

Several studies have evaluated the application of spatial interpolation methods for predicting contamination in multiple environmental medias. Hunova et al. (2011) used 11 different spatial interpolation methods to develop 1 km x 1 km resolution maps of mean vegetation season $O_3$, and Above Ozone Threshold of 40 ppb ($AOT_{40}$) for forested areas in the Cech Republic. One hour mean $O_3$ measurements from 24 monitoring stations were used to calculate both the seasonal $O_3$ mean and $AOT_{40}$ at each monitoring station (Hunova et al., 2011). The calculated values were subsequently used as input data for each interpolation method. The 11 interpolation methods (table 4.1) can be summarized into two categories: Category 1: Three different methods (IDW, RBF, and kriging) used only the 24 input points, and Category 2: Combined the input points with supplementary altitude data to develop a linear regression analysis and used spatial interpolation for subsequent residuals. (eight methods total) (Hunova et al., 2011). Of the 11 methods, linear regression of the input points with altitude, and subsequent interpolation of residuals with ordinary kriging (LR+res_OK), and interpolation of mean afternoon $O_3$ concentration with ordinary kriging minus regression of mean $O_3$ afternoon increment with altitude with subsequent interpolation of its residuals by ordinary kriging (ALR+res_OK) demonstrated the most potential with cross validation root mean square (RMSE) values for mean seasonal $O_3$ of 3.23 ppb for both methods (Hunova et al., 2011). (Table 4.1 and Figure 4.5). Results from this study demonstrate two effective interpolation techniques that can be used to interpolate and predict the spatial distribution of $O_3$ when monitoring sites are sparse. The previously discussed study
conducted by Peng et al. (2016) provides an example of using LUR analysis for spatial interpolation. As discussed in the previous section, the goal of this study was to develop a predictive model which maps the spatial distribution of heavy metals As, Cr, Pb, Cu, Ni and Zn in Qatari soils. The predictive model was created using the statistical software Cubist which was created by Rulequest© (Peng et al., 2016). The model used condition-based rules, and model attributes consisted of sample data from 300 surface soil samples, satellite images from January, February, April, May, June, July, August, September, and October (including remote sensing data for each image) from Landsat 8, and geopedological, geomorphological, and anthropological data (Peng et al., 2016). The details of the remote sensing data were discussed in the previous section. Geomorphological data included 30-meter (m) raster data displaying elevation, slope gradient, slope aspect, and distance to a drainage area. The geopedological data consisted of soil maps for the study area. Anthropological data included 30 m raster data displaying proximity to roads, night light image, and distance to environmental hotspots (i.e. wastewater treatment plants and solid waste dumping sites) (Peng et al., 2016). (Refer to Figure 4.7 in the Appendix for maps of each environmental variable). The algorithm produced by the model is based on the combinations of multiple linear regression models between the sample data and the remote sensing, geomorphological, geopedological data, and anthropogenic data. The linear regression models determine the importance of each variable with respect to the final predictive algorithm (Peng et al., 2016). (Figure 4.6 in the Appendix provides an example of a rule used for Ni predictions). Results showed that the model demonstrated good predictive capabilities for all elements. Of all of the prediction results, Cu had the highest $R^2 = 0.74$, followed by As > Pb > Cr > Zn > Ni. (Peng et al., 2016) (Figure 4.8). This study demonstrates how powerful statistical software can be used to develop accurate LUR models based on many environmental variables, and remote sensing data. Knibbs et al. (2014) developed a LUR model to predict NO$_2$ concentrations in Australia. The model, which was capable of national spatial coverage, used remote sensing data, and other land use predictor variables including proximity to major and minor roads, and impervious surfaces (Knibbs et al., 2014). A total of 315 independent variables (13 variables calculated at 22 buffers each), and 29-point variables were determined at, and around 68 monitoring sites with previous measured NO$_2$ values which were used to build the prediction model (Knibbs et al., 2014). Two different models were built: one for predicting annual average NO$_2$ concentrations from 2006-2011, and one for predicting monthly average NO$_2$ concentrations for each of the 72 months within that same time frame (Knibbs et al., 2014). The best annual model explained 81% ($R^2 = 0.81$) variability in measured NO$_2$ concentrations, and the best monthly model explained 76% ($R^2 = 0.76$) of the variability in NO$_2$ measurements (Knibbs et al., 2014). The models were applied to predict NO$_2$ concentrations at approximately 350,000 census mesh blocks. Weighted average concentrations ranged from 7.3 ppb in 2006 to 6.3 ppb in 2011(Knibbs et al., 2014). This study demonstrated how interpolation using LUR can produce accurate models capable of covering a large spatial area with usable spatial resolution (i.e. one census mesh block).

The studies discussed in this section demonstrate the significant potential for spatial interpolation methods, particularly LUR, to provide accurate exposure concentration predictions at usable spatial resolutions. This may become an invaluable tool to meet the goal of estimating exposure concentrations with significantly finer spatial and temporal resolution which are more representative to receptor location and time compared to current methods.
Table 4.1 – Ranking of different O₃ interpolation technique to develop O₃ maps. Obtained from Hunova et al. (2011). (IDW - Inverse Distance Weighted; RBF - Radial Basis Function; OK – Ordinary Kriging; LR - Linear Regression; ALR - interpolation of mean afternoon O₃ concentration with ordinary kriging minus regression of mean O₃ afternoon increment with altitude; res – residual)

<table>
<thead>
<tr>
<th>Interpolation technique</th>
<th>2007</th>
<th>2008</th>
<th>Average</th>
<th>RMSE (ppb)</th>
<th>Ranking</th>
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<tr>
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<td>4.97</td>
<td>5.10</td>
<td>11</td>
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<tr>
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<td>4.69</td>
<td>4.80</td>
<td>10</td>
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<tr>
<td>OK</td>
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<td>4.67</td>
<td>4.70</td>
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<td></td>
</tr>
<tr>
<td>LR</td>
<td>3.45</td>
<td>3.30</td>
<td>3.38</td>
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<td>LR + res_IDW</td>
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<tr>
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<tr>
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<td>3.33</td>
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<tr>
<td>ALR + res_OK</td>
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<td>3.07</td>
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Seasonal O₃ mean (ppb)

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<th></th>
<th>2007</th>
<th>2008</th>
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<tr>
<td>2008</td>
<td></td>
<td>38.87</td>
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<tr>
<td>Average</td>
<td></td>
<td></td>
<td>39.51</td>
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Figure 4.5 – Spatial interpolation of mean O$_3$ concentrations, and AOT$_{40}$ concentrations using linear regression of the input points with altitude, and subsequent interpolation of residuals with ordinary kriging (LR+res_OK), and interpolation of mean afternoon O$_3$ concentration with ordinary kriging minus regression of mean O$_3$ afternoon increment with altitude with subsequent interpolation of its residuals by ordinary kriging (ALR+res_OK). Obtained from Hunova et al. (2011)
Figure 4.8 – Predicted maps (30-m resolution) of topsoil concentrations of Cr, As, Ni, Zn, Pb and Cu. Obtained from Peng et al. (2016).
4.1.1.3. Geographic Information Sciences

The studies that have been discussed in the previous sections have all relied on GIS software to display and analyze geospatial data, including spatial interpolation. For these reasons, GIS software is necessary for any geospatial method to be conducted. This section will be devoted toward an additional application of GIS to combine the results of geospatial analysis with population data to evaluate the exposure potential by nearby receptors. Figures 4.9 – 4.12 demonstrate a theoretical example of how GIS can be used to convert discrete air monitoring data from fixed air monitoring stations to a usable map depicting the potential risk to receptors. In this example, GIS was used to calculate the overall risk of PM$_{10}$ exposure in Somerset County NJ. Risk was determined by using the weighted sum overlay tool in ArcGIS to calculate the weighted sum of the exposure concentration (determined via IDW of PM$_{10}$ monitoring data), land use, and presence of sensitive populations (determined with census data). The end result is a risk value which is a function of exposure concentration, potential exposure frequency, and presence of sensitive populations.

Figure 4.9 – Left - Average annual PM$_{10}$ values from 17 fixed ambient air monitoring stations throughout NJ. Right – Map of Somerset County depicting average PM$_{10}$ values throughout the county. The PM$_{10}$ values were calculated using spatial interpolation via IDW for PM$_{10}$ data from the 17 air monitoring stations.
Figure 4.10 – left – Sample of methodology used to determine potential exposure frequency associated with each land use type that was part of the Somerset County land use data. Each land use was assigned a score representing both the land uses potential for outdoor exposure and the potential outdoor exposure duration of each land use. The exposure value was the product of both the “outdoor exposure” and “exposure duration”. Thus, a higher exposure value indicates a greater risk of PM10 exposure. Right – calculated “exposure values” are mapped for each land use type. Orange indicates a lower exposure value, while green indicates a higher exposure value.
**Figure 4.11** – left – Sample of methodology used to determine percentage of sensitive sub-populations within each census tract. Right – A map was developed ranking each census tract based on its percentage of sensitive sub-populations.

<table>
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<tr>
<th>TRACT</th>
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<th>SENSITIVE SUB POPULATION (PERCENT)</th>
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<tr>
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<td>52</td>
</tr>
<tr>
<td>46298</td>
<td>2391</td>
<td>48</td>
</tr>
</tbody>
</table>
Figure 4.12 – Risk values were calculated for Somerset County by using the weighted sum overlay tool. The value of each raster cell is a function of the weighted sum of the exposure concentration (Figure 4.9), potential exposure frequency (Figure 4.10), and percent sensitive subpopulation values (Figure 4.11) for that particular cell.

It is important to note that this example was designed for demonstration purposes only with a focus toward identifying a geospatial modeling procedure that can visually depict the results of an exposure assessment.
and is capable of characterizing exposure and risk across spatially heterogenous environments with limited
data. However, the data that were used and created is an oversimplification that is lacking the quality that
should be used if this technique were utilized for an actual exposure assessment. Specifically, the PM$_{10}$
spatial interpolation should ideally use a more sophisticated LUR model as discussed in the previous
section. In addition, all land use and census data should be accompanied with voluntary personal surveys
to ensure that the most accurate and recent data is being collected. Nevertheless, the example illustrated in
section demonstrates the potential of GIS to quickly and efficiently characterize risk and exposure by
analyzing datasets which are regularly available to the public.

An additional benefit of GIS has been the recent advancement of online GIS. Online GIS has allowed
geospatial data including sample and monitoring data, as well as results of geospatial interpolation to be
uploaded and overlaid onto web-based maps that can be viewed by anyone in the general public. Online
mapping will allow for exposure assessment data and results to be viewed and interpolate more quickly,
and by a much larger audience compared to current methods.

4.1.2. Ubiquitous Chemical Sensor Technologies

Geospatial technologies alone cannot be relied on to reach the goal of more spatially and temporally refined
exposure concentrations. To truly meet this goal, there must be a significant increase in the ability to screen
and measure environmental media for the presence of contaminants. The current instruments used to
complete this task are expensive and are typically only used in a case specific scenario (e.g. worker
protection, or to evaluate an environmental cleanup site). Therefore, there is a need for a new generation of
chemical sensors, that are low cost, light weight, and capable of being deployed more frequently, and on at
a much finer spatial resolution. A potential solution to meet this need is the use and development of
chemical sensors which rely on micro-electro mechanical systems and nano-electro mechanical systems.
These sensors rely on the evolving fields of micro and nano fabrication, which develop materials on the
atomic and molecular scale. Due to their small size, and high surface to volume ratio, miniature chemical
sensor systems can be incorporated onto nano and micro materials, creating inexpensive, miniaturized
chemical sensors capable of being deployed at a much higher spatial and temporal resolution compared to
current chemical sensors. Although the detection mechanisms vary based on the particular sensor, micro
and nano chemical sensors all work by detecting changes in physical or chemical properties between the
sensor prior to and following the introduction of the pollutant (Kumar et al., 2014). These physical and
chemical changes are then converted to an electrical signal by a transducer, the strength of which is
dependent on the concentration of the detected chemical (Kumar et al., 2014). Figure 4.13 depicts the
general mechanism of chemical nano or micro sensors. Specific examples of sensor types include chemical
gas sensors such as chemoresistive, capacitance, and solid electrolyte sensors which measure changes in
conductivity, capacitance, and redox, respectively, and optical sensors which rely on the ability of
molecules to absorb radiation at specific wavelengths (Kumar et al., 2014). For instance, CO$_2$, CO, and
CH$_4$ have a unique absorbing spectrum at 4.25, 4.7, and 3.3 μm, respectively (Kumar et al., 2014).

Micro and nanosensors are being developed that are capable of detecting chemicals in various
environmental media. Sensors capable of detecting air pollutant concentrations include the previous
mentioned chemical gas and optical sensors, along with tungsten doped niobium oxide nanorods for
detecting NO$_2$ (Figure 4.14) (Yu et al., 2017); and single walled carbon nanotubes (SWCNTs) for detecting
NO$_2$ and NH$_3$ (Das et al., 2015). Furthermore, much progress has been made in deploying these sensors in
the air as “intelligent dust” capable of remaining in the atmosphere for hours (Das et al., 2015).
Nanoparticles capable of detecting pollutants in water include graphene capable of detecting heavy metals
(Das et al., 2015 and Wu et al., 2012) and PCBs (Church et al. 2016), silver nanoparticles for detecting
Hg$^{2+}$ (Das et al., 2015, Wu et al., 2012 and Ahmed et al., 2014), and gold nanoparticles for detecting nitrate
and nitrite (Das et al., 2015, Daniel et al., 2009 and Yi et al., 2015). An additional benefit to micro and nanosensors is the potential of detecting multiple chemicals simultaneously due to ability of multiple sensors to be present on the same chip (NRC, 2012).

In order for micro and Nanosensors to reach their full potential, they must demonstrate the ability to detect pollutants and produce data with the same accuracy and quality as current laboratory methods. To this end, the first EuNetAir Air Quality Joint Intercomparison Exercise was organized in Aveiro (Portugal) from October 13 through 27, 2014. During this exercise, the capability of multiple micro sensors to detect and measure for CO, NO\textsubscript{x}, O\textsubscript{3}, SO\textsubscript{2}, PM\textsubscript{10}, PM\textsubscript{2.5} were compared to standard air quality reference methods (Borrego et al., 2016). The IDAD-Institute of Environment and Development Air Quality Mobile Laboratory was staged at a fixed location in the city center of Aveiro, and continuous measurements were obtained for CO, NO\textsubscript{x}, O\textsubscript{3}, SO\textsubscript{2}, PM\textsubscript{10}, PM\textsubscript{2.5} temperature, humidity, wind speed and direction, solar radiation and precipitation with standard equipment and reference analyzers (Borrego et al., 2016). Sensor from multiple microsensor systems collocated with the reference analyzers, and data generated by each microsensor system was compared to the results generated by the reference analyzers (Borrego et al., 2016). The results indicated varying levels of success depending on the microsensor platform and on the sensors considered. There was a high correlation between results for O\textsubscript{3} (R\textsuperscript{2}: 0.12-0.77), CO (R\textsuperscript{2}: 0.53-0.87), and NO\textsubscript{2} (R\textsuperscript{2}: 0.02-0.89) and the reference analyzer results (Borrego et al., 2016). However, for PM (R\textsuperscript{2}: 0.07-0.36) and SO\textsubscript{2} (R\textsuperscript{2}: 0.09-0.20) the results showed low correlation coefficients between the reference and microsensor measurements (Borrego et al., 2016). Refer to figures 4.15 and table 4.2 for depictions and data summaries from this study.

Results from the EuNetAir Air Quality Joint Intercomparison Exercise indicate that for many micro and nanosensors limitations may still exist regarding accuracy. Despite some of these limitations, there is still tremendous potential for both micro and nanosensors for meeting the goal of determining exposure concentrations on a finer spatial and temporal scale. This potential is further magnified by incorporating these sensors into devices with GPS and transmitting the sensor data through a wireless network system (Das et al., 2015). This information will allow for near-real time pollution data to be viewed in multiple formats, including online maps, for multiple sensors and pollutants deployed at different locations (Das et al., 2015). Examples of wireless sensing networks will be discussed in section 4.1.3, and the use of GPS will be discussed in section 4.2.

Figure 4.14 – Scanning electron microscope (SEM) image of the tungsten doped niobium oxide nanorods at a scale of 1 µm (top right), 75 nm (top left) 1.5 µm (bottom), respectively. Obtained from Yu et al. (2016).
Figure 4.15 - IDAD-Institute of Environment and Development Air Quality Mobile Laboratory was staged at a fixed location and collocated with multiple microsensor systems during the 1st EuNetAir Air Quality Joint Intercomparison Exercise. Obtained from Borrego et al. (2016).

Table 4.2 – Statistical summary comparing the data from multiple microsensor platforms which were used during the first EuNetAir Air Quality Joint Intercomparison Exercise. Obtained from Borrego et al. (2016).
4.1.3. Wireless Monitoring Networks

Although the technologies and strategies discussed in Section 4 thus far demonstrate potential by themselves, perhaps the greatest potential will be realized by combining these technologies and strategies together to produce seamless monitoring networks capable of communicating the exposure concentrations of multiple environmental stressors at any location and time, along with alerts indicating unacceptable exposure risks. These monitoring networks could use online mapping and smart phone technology so that receptors would have the ability to see real-time exposure concentrations at any location. The development of these wireless networks is already underway, and two current examples include the Air Quality Egg Network in the United States, and the airTEXT program in the Greater London area. Air Quality Egg, which is manufactured by Wicked Device located in Ithaca, NY, is a community-based air monitoring network which uses individual units (eggs) equipped with light scattering and electrochemical sensors to measure CO, SO₂, VOC, PM₁₀, PM₂.₅, O₃, and NO₂ in both outdoor and indoor environments (Wicked Device, 2018). Each unit is capable of transmitting a Wi-Fi signal which publishes the real-time measurements to the air quality egg servers (Wicked Device, 2018). The air quality data of all participant units can then be viewed on an app in multiple formats, including maps, charts and tables (Figure 4.16). airTEXT provides online maps and data of hourly concentrations for NO₂, PM₁₀, PM₂.₅, and O₃. Unlike Air Quality Egg, airTEXT relies on data from weather forecasts, traffic patterns, and atmospheric conditions to create an air dispersion model. Air dispersion models are mathematical models which use the physical and chemical characteristics of the pollutant, and the surrounding environment to predict how the pollutant will disperse in the ambient atmosphere. These predictions made by airTEXT are compared to ground measurements, and the comparison statistics are available online (airTEXT, 2018). Both of these wireless monitoring networks rely on location tracking technologies with two different forms of exposure concentration measurements technologies. Air Quality Egg relies exclusively on measurements obtained from individual chemical sensors while airTEXT relies primarily on dispersion modeling. Ideally, the most reliable method would be one that combines the two methods and incorporates geospatial interpolation for areas with limited data. Such a method would involve the deployment of chemical sensors. Data from the sensors could then be used with atmospheric data to construct dispersion models to estimate the dispersion of pollutants throughout the atmosphere. Spatial interpolation could then be used to predict concentrations where sensor data is limited. Furthermore, while it is important that all technologies and strategies identified in this section continue to improve, improvement in ubiquitous sensing is perhaps the most important, because it provides a direct measurement of a contaminant at a specific time and location. Therefore, improvements specifically in the ability to dramatically increase the deployment and spatial coverage of these sensors would result in more accurate geospatial interpolations models based on more input points (i.e. sensor data).
4.1.4 Biomonitoring

The technologies discussed in Section 4 thus far are based on determining potential doses. However, the actual target dose received by a receptor is a function of both the potential dose and ADME characteristics of that particular stressor. For this reason, the most direct method of determining receptor exposure and dose would be obtaining a biological sample and observing specific biomarkers indicative of exposure. Obtaining this data quickly and efficiently has been difficult in the past. However, new biological screening techniques such as “lab-on-a-chip” and robust biomonitoring data sets such as the NHANES, have the potential to provide biological data where direct observations and measurements indicating exposure can be made. Lab-on-a-chip is a technology that uses the nano and micro sensing technologies discussed in section 4.1 to analyze biological samples such as blood, fluid, plasma and saliva for biomarkers of interest (Mehta, 2008). Lab-on-chip technology is based primarily on microsystems that incorporate microelectronic sensors and biological components onto a handheld device (Mehta, 2008). Such devices are currently under development in many parts of the world and are expected to become more commercially available in the near future (Mehta, 2008). A review conducted by the National Institute for Public Health and the Environment in 2013 identified 154 lab-on-a-chip devices from 75 different manufacturing companies (National Institute for Public Health and the Environment, 2013). Although many of these
devices are capable of detecting ions and small molecules in biological media, they’re primary use is to detect biomarkers of disease rather than exposure to environmental toxicants (National Institute for Public Health and the Environment, 2013). However, there is ongoing research to develop micro and nano chemical sensors capable of detecting biomarkers of environmental toxicant exposure, including, lead and organophosphate pesticides (Barry et al., 2009). Potential uses of lab-on-a-chip technology in exposure assessment could include, rapid screening of receptors in areas of concern where the use of other technologies has identified harmful exposure concentrations. The efficient screening methods of lab-on-a-chip technologies could make it possible to perform tests for multiple stressors in a relatively short period of time.

Another effective emerging strategy in biomonitoring is the use of large datasets of biomonitoring exposure data to develop exposure models based on actual doses, and to evaluate overall exposure trends. Examples of large biomonitoring datasets include, the National Children’s Study started by the CDC in 2000 with the goal of identifying and environmental exposures in children from birth to adulthood (NRC, 2012), and the NHANES National Reports on Human Exposure to Environmental Chemicals (NER) (Sobus et al., 2015). The NER is a periodic report of NHANES data which consists of human chemical biomarker results for various chemical biomarkers (Sobus et al., 2015). The most recent NER included biomonitoring data for 265 chemical biomarkers, a significant increase from the first NER in 1999 (Sobus et al., 2015). Particular of NHANES data in environmental assessment includes the construction of reverse exposure models which reconstructs exposure and dose from biomonitoring data (Sobus et al., 2015). An example of using NHANES biomonitoring data to construct a reverse exposure model is a study conducted by Wambaugh et al. (2013). In this study, exposures and intake dose were reconstructed from urinary concentrations of 82 NHANES chemicals (Wambaugh et al., 2013 and Sobus et al., 2015). These results were than used to calibrate predictions from more traditional far-field mass balance human exposure models. Reverse exposure modeling can also be used to directly compare biomarker levels to toxicological benchmarks such as NOAELs or RfDs (Sobus et al., 2015). An example based on reverse modeling was demonstrated by Blount et al. (2007), who used urinary perchlorate data from NHANES to reconstruct total daily doses which were subsequently compare to the perchlorate RfD. (Blount et al., 2007 and Sobus et al., 2015). Another study demonstrating the use of comparing NHANES data directly to toxicological benchmark levels was conducted by Kirman et al. (2012). In this study NHANES biomonitoring data for VOCs in blood were compared with recently derived screening biomonitoring equivalent (BE) values (Kirman et al., 2012). A BE is defined as the estimated concentration or range of concentrations of a chemical or its metabolites in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guidance value (Kirman et al., 2012). Blood concentrations of VOCs from the NHANES data set were compared with predicted screening BE values. HQ were calculated for individual chemicals, and a hazard index (HI) was calculated for combined exposures (Kirman et al., 2012). Results indicated that HI values for detected chemicals were generally at or below a value of 1, suggesting that the potential for deleterious effects was low (Kirman et al., 2012). In addition, detected levels of benzene in non-smokers were within the range of BE values corresponding to a $10^{-6}$– $10^{-4}$ range for upper-bound cancer risk. (Kirman et al., 2012). However, benzene levels in smokers were at the upper end of or exceeded the range, suggesting that smoking was an important determinant of HI and HQ values, (Kirman et al., 2012).

A study by Park et al. (2014) demonstrated how NHANES biomonitoring data could be used to construct a model capable of evaluating exposure to multiple environmental stressors. In this study, NHANES data was used to evaluate 134 environmental stressors in relation to serum lipids (total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides) (Park et al., 2014). The study identified 13 associated pollutants for total cholesterol, 9 for HDL, 5 for LDL and 27 for triglycerides (Park et al., 2014). Using the regression coefficients (weights) from joint analyses of the
combined data and exposure concentrations, Environmental Risk Scores (ERS) were calculated as a weighted sum of the stressor levels (Park et al., 2014) (Figure 4.18). ERS values were computed for multiple lipid outcomes examined individually (single-phenotype approach) or together (multi-phenotype approach) (Park et al., 2014) (Figure 4.18). Further evaluation of the calculated ERS values indicated that there were relatively stronger associations between ERS and lipid outcomes than with individual pollutants (Park et al., 2014). Results from this study suggests ERS is a promising tool for characterizing disease risk from multi-pollutant exposures (Park et al., 2014).

Biomonitoring strategies and technologies discussed in this section have the potential provide valuable biomarker data of actual exposures to the exposure assessment process. Information obtained from this biomonitoring data along with exposure models created from it can be used to further evaluate populations where less intrusive technologies discussed in sections 4.1.1-4.1.3 have identified potentially harmful exposures.

Figure 4.17 – Cells being sorted with electrical forces on a lab-on-a-chip. Obtained from Mehta et al. (2008).
Figure 4.18 – Schematic plot of Environmental Risk Score (ERS) calculation in study conducted by Park et al. (2014). Obtained from Park et al. (2014).
4.2. Estimating Exposure Frequency and Duration

The technologies discussed in section 4.1, specifically 4.1.1 through 4.1.3 are only useful if equally effective technologies exist that are capable of determining when, where, and for how long (i.e. exposure frequency and duration) a receptor comes into contact with a particular environmental stressor. Both exposure duration and frequency are functions of time and location. It is for this reason that emerging exposure frequency and duration technologies and strategies focus on accurately tracking a receptor’s indoor and outdoor location. This has been a challenge in traditional exposure assessments where tracking the time and locations of small cohorts is accomplished by assigning time/location/activity diaries, and tracking the time and location of larger cohorts on the population level typically relies on determining if a receptor’s home or work location is within a broad area of concern which has been delineated based on static monitoring or sampling. Due to the larger cohort size, the daily receptor movements in and out of various indoor and outdoor locations is typically not tracked for exposure assessments conducted on the population level. In addition, to more accurately track a receptor’s location, the ability to better estimate a receptor’s activity level is desirable, specifically when evaluating exposure to air pollutants. Activity rate is directly connected to inhalation rate, and therefore, an increase in activity will result in an increased potential dose if that activity is occurring at a location where there is an exposure concentration of concern.

There are several emerging technologies for characterizing exposure frequency and duration including the use of GPS, WPS, Bluetooth, accelerometers, and smart phone sensors, and strategies for effectively using these technologies including development of prediction models for micro locations and dose.

Over the last three decades, GPS technology has evolved from a purely government and military application to a usable format that is readily available and usable to nearly every member of the public. The use of GPS is advantageous during exposure assessment because it has the ability to collect continuous locational data that can be a direct indicator of a receptor’s location, and the frequency, and duration spent at each location. In addition, the use of GPS is not subject to the potential human error that exists with current time/location diaries used during many exposure assessments. An example of the advantages of GPS compared to time/location diaries was demonstrated in a study conducted by Elgethun et al. (2007) where time and location data recorded by a GPS tracking device was compared to National Human Exposure Assessment Survey (NHEAS) diaries. In this study 31 children ages 3–5 years old wore a GPS tracking device for the hours which they were awake. During the same time frame, their parents completed the NHEXAS diary timeline to document the time and location patterns of each child (Elgethun et al., 2007). Results revealed that the NHEXAS diaries misclassified child time and location patterns approximately 48% of the time compared to GPS data (Elgethun et al., 2007). Furthermore, the NHEXAS diaries underestimated the time children spent in the home by 17%, and overestimated time spent indoors at other locations, outside at home, outdoors in other locations, and in transit (Elgethun et al., 2007). Results from this study demonstrate the advantages to using GPS tracking devices over traditional time/location diaries to more accurately determine the time and location patterns of small cohorts and minimize the misclassification of exposure to both indoor and outdoor environmental stressors. These advantages will only increase as these devices decrease in size and become more user friendly. A more direct example of how inaccurately characterizing time and locations can result in misclassifying exposure is presented in a study by Dewulf et al. (2015). This study used GPS and accelerometer data on 180 participants ages 58 to 65 to compare the differences in the potential dose of when location and ventilation rate is taken into account compared to the traditional static method that just use NO$_2$ concentrations in the home (Dewulf et al., 2015). The study used three different methods to calculate the dose of inhaled NO$_2$: (1) The traditional static method where dose was calculated using only the NO$_2$ concentration in the home (2) Using a GPS, the dose of inhaled NO$_2$ is calculated by taking into account the locations of the individuals; (3) Using an accelerometer and GPS, dose of inhaled NO$_2$ is calculated by taking into account the location and ventilation rates (Dewulf et al., 2015). For all
methods, NO$_2$ concentration was obtained from a 10 m resolution LUR model of the entire country of Belgium (Dewulf et al., 2015). Results revealed that considering both location, and location with ventilation rate result in a difference in the calculated potential NO$_2$ (Dewulf et al., 2015). The difference in average inhaled NO$_2$ between methods 1 and 2 was a 1.74% decrease most likely attributed to individuals living in an area of higher contamination traveling outside of their homes to areas of lower contamination (Dewulf et al., 2015). The difference between method 1 and 3 was a 12.81% increase of inhaled NO$_2$ (Dewulf et al., 2015). The difference in the absolute value of mean inhaled NO$_2$ is even greater between individuals then the overall mean values which were used during the study, suggesting that the differences of 1.74% and 12.81%, may have a larger impact on an individual level (Dewulf et al., 2015). The results from this study demonstrate how the use of GPS and accelerometer data along with LUR modeled air exposure concentrations can provide an accurate and cost-effective means of determining potential dose to air pollutants. Refer to figures 4.19 - 4.21 for additional information from this study.

The studies conducted by both Elgethun et al., 2007 and Dewulf et al. 2015 present compelling cases for using GPS to determine exposure frequency and duration for exposure assessments. However, a significant limitation to GPS is its inability to function indoors. This is an important limitation, because many exposures to stressors occur inside rather than outside due to presence of harmful chemicals combined with low air circulation. In addition, GPS signal can be lost in outdoor locations in the presence of trees, buildings or other large objects which block and deflect satellite signals. Therefore, it is imperative that emerging strategies and technologies are developed which are capable of distinguishing indoor locations from outdoor locations. An example of such a technology that already exists is the use of bluetooth tags. This system works by establishing bluetooth beacons throughout an indoor location which send a bluetooth signal to a receiver which is typically an app on a user’s cell phone. The receiver then runs software which is capable of calculating the indoor locations based on the signal data from each beacon. Another example of technology that is capable of determining indoor locations is MicroTrac which was developed in a study by Breen et al. (2014). MicroTrac is a classification model which employs a decision tree (Figure 4.22) to predict a receptor’s location, and the frequency, and duration spent at each location. (Breen et al., 2014). An additional advantage to MicroTrac is that the ME model uses the same process to determine location when GPS signal is not available (Breen et al., 2014). In this study, MicroTrac was used on a cohort of nine participants. GPS data was collected for each participant for a continuous 24-hour period. Seven participants collected GPS data on a workday (five in summer, two in fall), and two participants collected GPS data on a non-workday (one in summer, one in fall) (Breen et al., 2014). Sample data collected from each GPS was processed in the MicroTrac model to determine the time spent in eight different MEs: 1) indoors at the participant’s home (Home-In); (2) outdoors near the participant’s home (Home-Out); (3) indoors at the participant’s workplace (Work-In); (4) outdoors near the workplace (Work-Out); (5) indoors at the school of the participant’s children (School-In); (6) outdoors near the school (School-Out); (7) inside a vehicle (In-Vehicle); and (8) Other (Breen et al., 2014). For comparison purposes, each participant also maintained a time/location/activity diary which was validated manually with each participants GPS data (Breen, 2014). The results of the time/location/activity diaries were compared to the MicroTrac estimates to determine the accuracy of the predictions (Breen, 2014). Results revealed impressive accuracy with MicroTrac correctly classifying the ME for 99.5% of the daily time spent by the participants (Breen et al., 2014). The use of MicroTrac could help to reduce the time–location uncertainty during exposure assessments. Furthermore, MicroTrac demonstrates potential for supporting large GPS data from widespread sensor networks (Breen et al., 2014). MicroTrac could also be used on a population level with GPS data obtained from smartphones (Breen, 2014). Large sets of GPS data collected with low participant burden could be classified in various MEs by MicroTrac to increase the sample size and update the older diary data in the time–activity databases (e.g., Consolidated Human Activity Database), which are used for
An example of a different technique to distinguish indoor from outdoor locations was presented in a study Anagnostopoulos et al. (2017) where smart phone sensors including barometric pressure, ambient light, accelerometer, global systems for mobile (GSM) tower signal strength and proximity, cloud coverage, time of day, GSM neighboring tower signal strength, magnetometer, ambient noise, and WiFi access networks (APs) were used to develop three different classification models using the Weka machine learning tool box software (Anagnostopoulos et al., 2017). A total of 11 participants were part of the study (Anagnostopoulos et al., 2017). Participants used their personal android smart phones as their primary data collection device, and a secondary phone was used to record when each participant entered indoors or outdoors via an app (Anagnostopoulos et al., 2017). The data generated by the secondary phone was used to determine the accuracy of the prediction (Anagnostopoulos et al., 2017). Each subsequent model that was created used less sensors than the previous model to determine not only the model’s accuracy, but also its energy usage (Anagnostopoulos et al., 2017). Results showed that the prediction accuracy, and transition accuracy were both high for all three models when all the data associated with each model is used (Anagnostopoulos et al., 2017). However, when subsampling the data, both the prediction accuracy, and the transition accuracy can drop below 50% (Anagnostopoulos et al., 2017). Results from this study indicate that there is still room for progress to made regarding the use of cell phone sensors to predict indoor vs outdoor locations. Specifically, in creating prediction models capable of high accuracy for outside data which was not used for model calibration. However, the potential benefits to using smart phone data to determine location are significant, because the method requires little to no additional resources. The study conducted by Anagnostopoulos et al. (2017) also was unique in that it evaluated the concept of using Wifi AP locations to determine an individual’s location. This concept, known as WPS, is a somewhat novel concept, however it could potentially play a significant role in exposure assessment by being able to identify a receptors indoor location. A study conducted by Su et al. (2014) further demonstrated the use of WPS via smart phone data to more accurately to determine location. In this study, the exposure of one receptor to NO$_2$ was evaluated during a three-month period by using smart phone momentary services provided by Google (Su et al., 2014). For the purposes of this study, location was determined by public Wifi networks rather than GPS (Su et al., 2014). The address of the individuals home, and work, as well as his commute route was obtained for location classification purposes (Su et al., 2014). In addition, the commute route was used along with the home departure and office arrival times to interpolate the individual’s space-time while commuting (Su et al., 2014). NO$_2$ concentrations were obtained from a NO$_2$ pollution surface model created through LUR (Su et al., 2014). In addition, two indoor/outdoor infiltration adjustment factors were used (1.33 and 5.00) to account for concentration differences in NO$_2$ between indoor and outdoor locations. These values represented median and middle high end indoor/outdoor NO$_2$ ratios from previous literature. Daily air pollutant concentrations for the individual were calculated by superimposing the LUR surface over daily location data collected through the smart phone. Three different exposure calculations were used: (1) the traditional way of assigning exposure was applied, i.e., using home address as a single location of exposure. (2) Time-weighted average pollution exposures were calculated using all the location data, but assuming that time has a linear relationship to total exposure. (3). Time and concentrated weighted pollution exposure was calculated using all the location data and considering the cumulative impacts of both time and concentration (Su et al., 2014). Cumulative exposure results ranged from 21.01 ppb when exposure was calculated using only the home address to 96.49 ppb when time and concentrated weighted pollution exposure was calculated using all the location data and considering the cumulative impacts of both time and concentration. The latter exposure value is 359% higher. These results indicate that when momentary location, and indoor/outdoor air infiltration are considered, the individual's cumulative exposure could be substantially different from the exposure estimated using ambient concentrations at the home location alone. This study demonstrates the potential of using WPS to determine exposure location, and the
significant difference in estimates when a receptor’s location is accurately tracked. In addition, this study presents simple way to integrate momentary location and indoor-outdoor air exchange into the exposure calculation.

The studies discussed in this section demonstrate how the continued evolution of location tracking technologies can potentially generate more accurate exposure frequency and duration exposure assessment data compared to current methods. Of particular significance, is the potential to locate indoor locations, and to track when a receptor travels between an indoor and outdoor location. Successfully distinguishing between indoor and outdoor locations would allow risk assessors to generate more refined exposure frequency and duration estimates based on more realistic spatial and temporal patterns of mobile receptors. However, as promising as some of the technologies and strategies discussed in this section may be, they must be implemented with a level of caution in regard to personal privacy. It is recommended that the most potentially intrusive location tracking methods only be utilized when necessary for small populations of concern.

![Figure 4.19 – Equations used by Dewulf et al. (2015) to calculate dose. Equation 1 only considers the NO\textsubscript{2} concentration in the receptor home. Equation 2 considers the NO\textsubscript{2} concentration at location that the receptor travels to, and equation 3 considers the receptors location and ventilation rate. Obtained from Dewulf et al. (2015).](image-url)
Figure 4.20 - Map depicting the GPS locations of each receptor and their associated ventilation rate overlaid on a base map of NO₂ concentrations which were determined with LUR. Obtained from Dewulf et al. (2015).
Figure 4.21 - Map depicting the GPS locations of each receptor and their associated mean inhaled NO$_2$ dose which was calculated using both location and ventilation rate overlaid on a base map of NO$_2$ concentrations which were determined with LUR. Obtained from Dewulf et al. (2015).
4.3. Research Needs

The studies in Sections 4.1 and 4.2 indicate that substantially more progress has been made in developing and advancing exposure assessment technologies for air pollutants compared to pollutants in water and soil. This is most likely due to the relative ease in which air monitoring networks based on fixed monitoring stations can be deployed compared to that for water and soil. In addition, contaminants generally move more quickly through air compared to water where movement of contaminants can vary greatly depending on the contaminant solubility, or soil where contaminants tend to remain fixed (e.g., bound) or move slowly via erosion, degradation and transformation process. Differences in contaminant movement in water and soil make it difficult to obtain sample and monitoring information at the spatial scale of air monitoring. In the case of soil contaminants, further evaluation would require a substantial amount of data from private properties and other locations where physical access could frequently be difficult. However, in order to meet exposure assessment goals outlined in the beginning of this section, it is imperative that there are developments for water and soil pollution monitoring networks that are on par with current developments.
in air monitoring networks. Soil and water networks would greatly benefit from improvements in the measurement, deployment, and price of chemical sensors. These improvements could lead to an influx in soil and water contaminant data. The incorporation of GPS into sensors would allow for this data to be geocoded. Wireless monitoring networks or online communities could be used as central locations to load sample data from various locations onto an online portal. The data could then be incorporated into online maps, and spatial interpolation (as discussed in Section 4.1.1.2) could be used to fill in the spatial gaps. Although this process would not be as instantaneous as air monitoring, it would provide an improvement over the current methods of measuring and sharing water and soil pollution data, and potentially make it easier to more quickly identify exposure areas of concern.

5. Summary and Conclusions

Table 5.1 lists the current risk assessment limitations and uncertainties depicted in Figure 2.2, and then describes the potential remedies for those uncertainties and limitations based on the emerging techniques and strategies discussed in Sections 3 and 4. In summary, the uncertainty in the current toxicity assessment begins with a hazard identification step that typically identifies apical toxic end points from controlled laboratory animal toxicity studies which use higher acute doses rather than the lower chronic doses that are typical of human exposure to environmental toxicants. Utilizing this toxicity data in the dose-response assessment step results in the use of generic UF$s to account for dose extrapolations, and/or species scaling for non-carcinogens, and in low dose extrapolations and species body weight scaling to reconcile differences in exposure levels when evaluating a carcinogen. Furthermore, use of toxicity data with acute doses, results in RfDs for noncarcinogens that are based on threshold doses that are established at non-linear PODs for apical toxic end points, such as tissue or organ toxicity. Therefore, the process does not capture non-threshold effects or toxic end points associated with lower chronic doses, such as cytotoxicity. In addition, current toxicity assessment methods do not account for variation in receptor susceptibility factors. For these reasons, emerging techniques and strategies are focused on generating toxicity data that use human cells to evaluate toxic end points that occur at the lower chronic doses. This new toxicity data can be generated by relying on in vitro HTS toxicity testing using human cells lines to determine the cytotoxic effects that occur from perturbations of toxicity pathways by environmental toxicants at various doses. The increased speed and efficiency of in vitro HTS along with use of large databases such as ToxCast to house in vitro test results, will dramatically increase the efficiency and consistency of the hazard identification step, and allow for the toxicity assessment of new chemicals and re-evaluation of toxicants with limited data. During the dose-response step, PBPK based reverse dosimetry modeling could be used to calculate the internal dose associated with in vitro cytotoxic end points based on toxicant specific ADME properties. In addition, VTs could be used to evaluate and interrupt the effects of doses associated with in vitro toxicity pathway perturbations on multiple levels of biological organization to ensure that the most sensitive AOPs are being evaluated. Lastly, genetic biomarker analysis of biological samples from more susceptible populations serves as a potential solution for ensuring that these receptors are not being exposed to unacceptable levels of environmental toxicants.

Uncertainty in the current exposure assessment approach is related to the inability to generate exposure concentrations that are spatially and temporally representative, and to accurately determine exposure factor data and characterize variability in exposure factors for exposed receptors. For these reasons, emerging techniques and strategies will focus on producing near-real time exposure concentrations at a finer spatial resolution, tracking the movement of receptors throughout all indoor and outdoor microenvironments, and when necessary, quickly screening biological samples of exposed populations. The development of light weight, low cost and GPS equipped chemical sensors which use nano-electric and micro-electric technology will allow risk assessors, environmental professionals and even members of the public to quickly and frequently screen environmental media for contaminants of concern. If successfully implemented, this process would produce significantly more exposure concentration data compared to current methods. In locations where it is still difficult to directly measure exposure concentrations, geospatial technologies...
including remote sensing and spatial interpolation with GIS can be used to provide exposure estimates based on the surrounding measured concentrations, and any influential environmental variables. Furthermore, GIS can be used to incorporate exposure concentrations with receptor data to efficiently produce exposure maps to aide assessors and the public in quickly determining geographic areas of concern. Data from chemical sensors and geospatial analyses can then be uploaded by multiple users and organizations onto seamless online monitoring networks. These online monitoring networks would therefore be capable of communicating near-real time exposure data for multiple environmental stressors at any location and time, along with alerts indicating potentially unacceptable exposure risks, which could further streamline on the ground sampling and data collection methods. Along with more accurate exposure concentration data, increase use of GPS technology, as well as developments in bluetooth tags, WPS, and computational models based on cell phone data will allow assessors to track receptors throughout all microenvironments, including indoor environments. Lastly, lab-on-a-chip devices can be used for rapid screening of receptors in areas of concern where the use of other technologies has identified harmful exposure concentrations.

Table 5.2 provides an example of a theoretical “tool box” that could be used by a risk assessor to quickly identify an emerging strategy or technique that may be of use for a particular risk assessment. This “tool box” or a similar system could serve as a practical resource to risk assessors interested in using new risk assessment techniques, but who do not have the time and resources to thoroughly search for techniques that meet their particular needs. Use of such a resource would be most valuable during the anticipated transition period that will occur as newer risk assessment methods, including those discussed in sections 3 and 4 gradually replace the current methods. It is anticipated that this process will be gradual to allow successful methods to be rigorously tested and validated, and for unsuccessful methods to be identified and either modified or eliminated. To this end, it is noteworthy to mention that the methods discussed in this paper represent a range of developmental progress. Methods such as VTs and micro/nano chemical sensors show promising potential but are still very much in their infancy in regard to use and development. Conversely, many geospatial and in vitro screening techniques are fairly well established, and additional potential will be realized by the expanded use of these techniques (e.g. using vitro studies to evaluate toxicity pathway perturbations). In addition, a pilot study that conducts an entire environmental risk assessment, including both the toxicity and exposure assessments, using the techniques and strategies discussed throughout this paper, and compares results to the same risk assessment using traditional methods would be beneficial in determining the benefits and limitations of newer methods.

Replacement of current risk assessment methods with newer risk assessment methods, including methods discussed in this paper, may eventually lead to changes in the structure of both the toxicity and exposure assessment components, which, ultimately, influence the overall risk characterization. In the case of toxicity assessment, it can be anticipated that the structure will still consist of separate hazard identification and dose-response steps. However, the replacement of traditional toxicity data with in vitro data, could lead to the development of large centralized databases to house in vitro results. An example of such a database already in existence is EPA’s ToxCast. In vitro data in these databases would be readily available to be downloaded by assessors, and subsequently used in VTs, PBPK based reverse dosimetry, and similar in vitro to in vivo models which will serve as the backbone of the new dose-response method.

Structural changes in exposure assessment may be more dramatic compared to toxicity assessment. The current exposure assessment method relies on a scenario-based structure where exposure assessments are typically only conducted under particular scenarios. Such scenarios may include, the construction of an environmentally regulated facility, or the discovery of contamination during property transactions. However, the emerging exposure assessment methods discussed throughout this paper suggest the possibility of a more integrated approach where near-real time exposure data are continuously uploaded to online monitoring networks that can be accessed by all members of the public. If implemented to its full potential, such an approach would represent a fundamental change in the exposure assessment process from a purely scenario-based process to a holistic approach based on constant near-real time monitoring of the
exposure conditions at all locations regardless of scenario. When exposure data from the online monitoring network identified geographical locations where exposures of concern exist, a more thorough exposure assessment using more intrusive methods such as indoor/outdoor receptor tracking or, when applicable biomonitoring via lab-on-a-chip would be conducted in that particular location. (Refer to Figure 5.1 for a conceptual model of this holistic exposure assessment). This more holistic approach would have several advantages over the current approach: 1. Thorough exposure assessments and potential environmental remediations would be based purely on exposure concentrations, rather than specific scenarios, therefore eliminating the potential of high risk locations from going undiscovered. 2. This method would ensure that expensive and intrusive resources would only be used at locations where they are necessary. 3. The general public would become more aware of the environmental exposure conditions near their home and work, which may prompt them to take a more proactive role in engaging in development and/or modification of environmental regulations in their community. Despite the potential for this new exposure assessment method there is still much work to be done, if such a system were to become a reality. The micro and nano chemical sensors that would serve as the basis of such a system are still very much in development, and data currently obtained from these sensors would not be considered reliable enough to be used for global monitoring and decision making. In addition, as was discussed in section 4, obtaining spatially ubiquitous monitoring data for soil and water contamination will be challenging due to the fate and transport properties of contaminants in water and soil, and the need for exposure concentration measurements to be collected from private property. Furthermore, the success of a holistic exposure assessment will be dependent on participation and contribution from both the public and private sector to ensure continued innovation of techniques and public participation.

This paper provides a thorough review of emerging risk assessment techniques and strategies that will potentially increase accuracy and efficiency in the risk assessment process. Emerging techniques and strategies in toxicity assessment are focused on using cytotoxicity data from in vitro HTS screening of human cell lines exposed to low doses of environmental toxicants, and subsequent PBPK models and VTs to evaluate in vitro data to in vivo conditions. These techniques and strategies should increase the efficiency and accuracy in the risk assessment process by replacing toxicity data from controlled animal laboratory studies that use high doses and apical end points, with human toxicity data based on toxic end points associated with lower chronic doses. Emerging techniques and strategies in exposure assessment include deploying light weight, low cost nano-electro and micro-electro chemical sensors to measure near-real time exposure concentrations at much finer spatial resolutions, and subsequent geospatial analyses to estimate exposure concentration in unmeasured locations. The use of publicly accessible online monitoring networks to upload, share and view exposure data will potentially make it easier to identify and mitigate areas of concern, and may eventually change the exposure assessment process from a strictly scenario-based process to a more holistic process. In addition, developments in tracking technologies will provide assessors with more accurate and receptor-specific data in regards to exposure frequency and duration. Furthermore, developments in biomonitoring technology, including portable and easy to use lab-on-a-chip devices will provide a method of obtaining direct receptor-specific doses from populations in areas where the use of less invasive methods has identified an exposure of concern. These emerging techniques and strategies should increase the accuracy and efficiency in the risk assessment process by replacing the current exposure assessment methods based on limited sampling, monitoring and exposure factor data with methods that will provide near real time exposure concentrations on finer spatial scale, and track exposure frequency and duration in both indoor and outdoor locations. Information obtained for this review indicates that the process of augmenting the current risk assessment methods with the newer methods discussed throughout this paper will be a gradual process that includes the further development, testing and validation of successful methods, and elimination of unsuccessful methods. For this reason, it is suggested that an environmental “tool box” or similar system be developed to provide an easy to use resource for risk assessors who are interested in using new risk assessment techniques but lack the time and resources to thoroughly search through all of the new emerging techniques and strategies.
<table>
<thead>
<tr>
<th>Risk Assessment Step</th>
<th>Uncertainty of Current Method</th>
<th>Potential Remedy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Identification</td>
<td>Extrapolation from acute dose animal studies</td>
<td>Use data obtained from HTS in vitro toxicity pathway testing</td>
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<tr>
<td></td>
<td>Studies with different results</td>
<td>Develop rich databases such as ToxCast with easy to obtained toxicity data from in-vitro tests which consistently evaluate cytotoxic endpoints.</td>
</tr>
<tr>
<td>Dose-Response</td>
<td>Detection of non-threshold and/or chronic adverse effects</td>
<td>Use in vitro toxicity data from human cell lines to evaluate cytotoxic endpoints associated with smaller doses.</td>
</tr>
<tr>
<td></td>
<td>Variations in receptor susceptibility factors</td>
<td>Use PBPK Based Reverse Dosimetry that take into account the specific ADME properties of an environmental toxicant in a human body to obtain the internal dose associated with a specific cytotoxic end points. Use of VTs to ensure that the most sensitive AOPs are being evaluated.</td>
</tr>
<tr>
<td>Exposure Assessment</td>
<td>Inadequate environmental or incomplete exposure information</td>
<td>Obtain biological samples from sensitive sub-populations and analyze samples for genetic biomarkers to ensure that cytotoxicity has not occurred.</td>
</tr>
<tr>
<td></td>
<td>Use of surrogate or inaccurate environmental or human exposure factor data</td>
<td>Use of light weight and low cost chemical sensors using nano-electro and micro-electro technology to quickly and frequently screen environmental media for contaminants of concern, producing significantly more exposure concentration data compared to current methods.</td>
</tr>
<tr>
<td></td>
<td>Characterization of environmental and receptor variability</td>
<td>Development of seamless online monitoring networks capable of communicating near-real time exposure data for multiple environmental stressors at any location and time, along with alerts indicating unacceptable exposure risks. Exposure data could be viewed in multiple formats on an online portal</td>
</tr>
<tr>
<td></td>
<td>Use of surroguet or inaccurate environmental or human exposure factor data</td>
<td>Use of spatial interpolation to estimate exposure concentrations at locations without sampling or monitoring data.</td>
</tr>
<tr>
<td></td>
<td>Characterization of environmental and receptor variability</td>
<td>Use or GPS to accurately obtain outdoor exposure concentrations and receptor locations, and bluetooth tags, WPS, and computational models based on cell phone data to obtain indoor locations.</td>
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<tr>
<td></td>
<td></td>
<td>Use of accelerometers and GPS to characterize exposure to air pollutants based on location and ventilation rate.</td>
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<td></td>
<td></td>
<td>Use of Lab-On-A-Chip to screen receptors in areas of concern where the use of other technologies has identified harmful exposure concentrations.</td>
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**Notes:** HTS - High Throughput Screening; QSAR - Quantitative Structure and Activity Relationships; PBPK - Physiologically Based Pharmacokinetic; ADME - absorption, distribution, metabolism and elimination; GIS - Geographical Information Science; IDW - Inverse Distance Weighted; LUR - Land Use Regression; GPS - Geographical Positioning System; WPS - Wifi Positioning System; Wifi AP - Wifi Access Points

Table 5.1 – Uncertainties and limitations of current methods in second column with the associated remedies, including emerging techniques and strategies summarized in this paper, in the third column.
<table>
<thead>
<tr>
<th>Risk Assessment Step</th>
<th>Tool</th>
<th>Description</th>
<th>Use</th>
<th>Relevant Citations</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>QSAR Models</td>
<td>Models that use a template chemical structure to predict how a toxicant’s physical and chemical properties will influence its stability in the environment, potential for exposure, route of exposure, bio accumulation potential, routes of metabolism, toxicity and metabolite toxicity.</td>
<td>Using HTS In-Vitro data for template chemicals, QSAR models can be used quickly evaluate the cytotoxic endpoints of of several environmental toxicants in a relatively short time span.</td>
<td>Mansouri et al. (2016). <a href="http://dx.doi.org/10.1289/ehp.1510267">http://dx.doi.org/10.1289/ehp.1510267</a></td>
</tr>
<tr>
<td>Dose-Response</td>
<td>PBPK Reverse Dosimetry Modeling</td>
<td>An internal or exposure dose is obtained from an in vitro concentration using mathematical equations to model the ADME characteristics of a toxicant in an organism.</td>
<td>To determine the internal or exposure dose associated with cytotoxic end points obtained from in-vitro data.</td>
<td>Louisse et al. (2017). <a href="https://pubs.acs.org/doi/10.1021/acs.chemrestox.6b00302">https://pubs.acs.org/doi/10.1021/acs.chemrestox.6b00302</a> DeJongh et al. (1999)</td>
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<tr>
<td>Exposure Assessment</td>
<td>GIS Software Geospatial Analysis - Mapping Exposure Potential</td>
<td>Combines geospatial data for exposure concentrations with population and land use data to spatially represent areas with the highest exposure potential.</td>
<td>Quick method to determine the geographical areas with the greatest risk of exposure, as well as areas where there is little risk.</td>
<td>Kumar et al. (2014). <a href="https://www.sciencedirect.com/science/article/pii/S0160412014003547">https://www.sciencedirect.com/science/article/pii/S0160412014003547</a></td>
</tr>
<tr>
<td></td>
<td>Ubiquitous Chemical Sensors</td>
<td>Low cost light weight chemical sensors which use micro-electro and nano-electro technology to quickly screen environmental media for contaminants of concern.</td>
<td>Due to the low cost and light weight features, these sensors can be deployed more frequently and on a much finer spatial scale than current chemical sensors.</td>
<td>Yu et al. (2017). <a href="https://www.sciencedirect.com/science/article/pii/S0925400516310346">https://www.sciencedirect.com/science/article/pii/S0925400516310346</a></td>
</tr>
<tr>
<td></td>
<td>Online Mapping and Wireless Networks</td>
<td>Combines geospatial and chemical sensor technologies to produce seamless monitoring networks capable of communicating the exposure concentrations of multiple environmental stressors at any location and time, along with alerts indicating unacceptable exposure risks.</td>
<td>Produces continuous near-real time exposure data at varying spatial resolutions that can be viewed in multiple formats on an online portal.</td>
<td>Borrego et al. (2016). <a href="http://dx.doi.org/10.1016/j.atmosenv.2016.09.050">http://dx.doi.org/10.1016/j.atmosenv.2016.09.050</a></td>
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<tr>
<th>Risk Assessment Step</th>
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<th>Use</th>
<th>Relevant Citations</th>
</tr>
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<tbody>
<tr>
<td>GPS Technology</td>
<td>Provides the real-time geographical location of a receptor when there is sufficient satellite signal.</td>
<td>When there is sufficient satellite signal, GPS data can collect continuous locational data that can be a direct indicator of a receptor’s location, and the frequency, and duration spent at each location.</td>
<td>Elgethun et al. (2007). Available: <a href="https://www.ncbi.nlm.nih.gov/pubmed/16773123">https://www.ncbi.nlm.nih.gov/pubmed/16773123</a></td>
<td></td>
</tr>
<tr>
<td>GPS and Accelerometer Data</td>
<td>Combines GPS Technology with accelerometer data to estimate potential exposure via inhalation based on location and ventilation rate.</td>
<td>Estimates potential exposure to air pollutants based on both location and ventilation rate.</td>
<td>Dewulf et al. (2015). <a href="https://doi.org/10.1016/j.jth.2015.10.004">https://doi.org/10.1016/j.jth.2015.10.004</a></td>
<td></td>
</tr>
<tr>
<td>Risk Assessment Step</td>
<td>Tool</td>
<td>Description</td>
<td>Use</td>
<td>Relevant Citations</td>
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<tr>
<td>Exposure Assessment</td>
<td>MicroTrac and similar models</td>
<td>Computational models that use GPS and/or smartphone data to determine a receptor's location, including indoor locations.</td>
<td>Can be used to accurately determine a receptor’s indoor and outdoor location, and the frequency, and duration spent at each location.</td>
<td>Breen et al. (2014). <a href="http://www.nature.com/articles/jes201413">http://www.nature.com/articles/jes201413</a></td>
</tr>
<tr>
<td></td>
<td>Bluetooth tags</td>
<td>Uses bluetooth beacons and a receiver (typically a cellphone) to establish an indoor monitoring network capable of determining indoor locations.</td>
<td>Accurately determines a receptor’s indoor location. Can also be used to accurately determine indoor sampling and monitoring locations.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WPS</td>
<td>Uses the Wifi AP locations to determine a receptors location, including indoor locations.</td>
<td>Can be used to accurately determine a receptor’s indoor and outdoor location, and the frequency, and duration spent at each location.</td>
<td>Anagnostopoulos et al. (2017). <a href="https://link.springer.com/article/10.1007/s00779-017-1028-y">https://link.springer.com/article/10.1007/s00779-017-1028-y</a> Su et al. (2014). <a href="http://dx.doi.org/10.1016/j.scitotenv.2014.11.022">http://dx.doi.org/10.1016/j.scitotenv.2014.11.022</a></td>
</tr>
</tbody>
</table>

Table 5.2 – Theoretical “Tool Box” that could be used by a risk assessor to quickly identify an emerging strategy or technique that may be of use for a particular risk assessment.
Figure 5.1 – Conceptual model of a holistic approach to exposure assessment based on an online monitoring network providing continuous near-real time exposure data.
6. References


43. Das S, Sen B, Debnath N. Recent trends in nanomaterials applications in environmental


50. Wicked Device, LLC. 2018; https://airqualityegg.wickeddevice.com/

51. Cambridge Environmental Research Consultants (CERC), Ltd. airTEXT. 2018; http://www.airtext.info/about


Appendix
Figure 3.2 – Example of a simplified toxicity pathway perturbation with liver cancer as a toxic end point. Obtained from Shah and Wambaugh (2010). Virtual Tissue Modeling in Toxicology.
Figure 3.3 – Toxicity pathway clustering based on chemical cytotoxicity kinetics data. a) Binary association between activities in pathways (rows) and chemical cytotoxicity kinetics groupings (columns). Magenta cell: significant; white cell: non-significant. n_in_bin: number of chemicals in the bin (grouping). b) Degree of association between the earliest time intervals where chemicals reached the maximum cytotoxic effect and activity in toxicity pathways. Red row text: stress response pathways; black row text: nuclear receptor related pathways; n: number of times of associations found in a); more intensified purple color, higher degree of association. This application helps researchers and risk managers determine the most important pathways to focus evaluative efforts. Obtained from Jui-Hua et al. (2017).
Figure 3.6 - Virtual tissue components. The vertical arrows at each step in the process reflect the iterative nature of model evaluating using experimental data. Obtained from Shah and Wambaugh (2010). Virtual tissues can be used to interpret how doses associated cytotoxic effects determined with in vitro data will impact higher levels of biological origination.
Figure 3.7 – Summary of how knowledge of environmental toxicant mode of action, effected cellular pathways, cellular end points and corresponding cellular interactions should be used to construct a VT model for evaluating liver cancer. Obtained from Shah et al. (2009). Virtual tissues can be used to interpret how doses associated cytotoxic effects determined with in vitro data will impact higher levels of biological origination.
Figure 4.3 – Global Aerosol Optical Depth (AOD) for September 2000 (top), September 2008 (middle), and February 2015 (bottom) from the MODIS remote sensing system. Obtained from nasa.gov
Figure 4.6 - Example of the rule used by Cubist software to predict the concentration of Ni. Obtained from Peng et al. (2016).

Rule 1: (126 cases, mean 11.4, range 3.0–33.4, estimation error 3.9)
If:
Soil type in \{1, 2, 3, 5\} (the numbers indicate different soil types in Qatar)
Jan_Band2 \_ 0.1645
Then:
\[ Ni = 6.8 - 13,238 \times \text{wetness (Jan)} - 10,271 \times \text{Band 6 (Jan)} - 7254 \times \text{Band 7 (Jan)} + 8651 \times \text{BCI (Jan)} - 2203 \times \text{Band 4 (Jan)} + 929 \times \text{Band 5 (Jan)} + 1305 \times \text{Band 2 (Jan)} - 379 \times \text{Band 4 (Feb)} - 255 \times \text{Wetness (Feb)} + 371 \times \text{Band 3 (Feb)}. \]
Figure 4.7 – Maps of the different environmental variables used to develop predictive model for soil heavy metals. Obtained from Peng et al. (2016).