

1           **Assessing Bioavailability as a Determinant of Pollutant**  
2                           **Exposure and Effects**  
3           ***Building a Multidisciplinary Paradigm for the 21<sup>st</sup> Century***  
4                           ***and Beyond***

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6                           **Final Summary**  
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9   Chemicals in the environment represent a risk to the extent that humans and other living  
10 organisms are exposed to these chemicals and that exposure leads to disease. Many of these  
11 chemicals interact with organic and inorganic matrices in soil and sediment by several  
12 mechanisms that impact the concentration that is available to impact the biology. Bioavailability,  
13 or bioaccessibility, of chemicals can be a major determinant of how compounds are transported  
14 within and between environments. Bioavailability can significantly influence exposure; how  
15 chemicals impact humans and other organisms; and how they behave inside organisms to  
16 result in disease(s) we associate with exposure. Existing regulatory documentation provides  
17 guidance on how bioavailability adjustments may be incorporated into the risk assessment  
18 process for humans and ecological receptors. However there is considerable uncertainty about  
19 how to incorporate bioavailability into the environmental and human health exposure and risk  
20 assessments, and how to make cleanup decisions based on these measures rather than total  
21 concentrations.

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23   This conference brought together researchers and regulators from environmental and medical  
24 sciences, public health, risk assessors, regulators, and remediators to establish common  
25 concepts; identify major systematic gaps in our knowledge of bioavailability and the implications  
26 of bioavailability; and to define and prioritize research needs. Because there have been several  
27 meetings and workshops addressing specific aspects of the bioavailability issue, the Steering  
28 Committee felt that this conference needed to take a broad approach to the topic and focus on  
29 major gaps in our knowledge and the best applications of our existing knowledge.

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31   The meeting consisted in part of formal presentations to bring the diverse audience to an  
32 understanding of the complex issues related to the different areas of bioavailability research  
33 important for defining risk. Especially important was the discussion within and between the  
34 different disciplines critical for making the links between chemicals in the environment,  
35 bioavailability, and individuals with disease.

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37   The discussions after the presentations and among the small groups identified common themes  
38 and research needs. The following report will first discuss the summary conclusions of the  
39 meeting and then address the specific research needs in a number of specific areas. This  
40 summary was prepared by Fred Pfaender with editorial input from the Steering Committee,  
41 especially Martin Alexander and Maureen Avakian.

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43   **Summary Conclusions:**  
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45   1.     There was general agreement that the scientific community is not using all the  
46 knowledge accumulated over the last twenty years to help make decisions for optimal site  
47 cleanup, estimating the health effects of exposure, or assessing risk. There has been  
48 significant progress in toxicology, occupational hygiene, soil and environmental sciences, and  
49 remediation technology. Often these findings do not work their way into the knowledge base of

1 related fields, much less into practice. New methods are emerging that specifically address  
2 chemical bioavailability, but they are only slowly working their way into the hands of those doing  
3 site assessment and cleanup. Individuals or organizations most involved in site cleanup have  
4 learned many lessons about what works and what does not. Much of this knowledge is  
5 documented in site records, but has not reached the risk assessment or research community.  
6 On many topics it was evident that we know more than we thought we did, but that this  
7 knowledge has not been synthesized in a meaningful way. There are clearly many gaps in our  
8 knowledge but they are hard to define because we do not have a cross disciplinary synthesis of  
9 what we do know. The need is for some group to convene to begin this synthesis.

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11 2. Related to the synthesis is the development of a comprehensive, internationally  
12 accessible, and easy-to-use database that contains the relevant information including at least  
13 site properties, human exposure data, ecotoxicology, and human health records from areas  
14 near sites. Such a database would have applications far beyond bioavailability adjustments.  
15 NIOSH and ATSDR are already assembling such data for worker exposure and blood levels of  
16 chemicals like lead. The scope of such efforts needs to be expanded. The information exists in  
17 many different places such as the peer-reviewed literature, site remediation reports and  
18 documents of state agencies and regional offices of federal agencies. Assembling this  
19 information will be difficult and time consuming, but it was felt by all to be essential for risk  
20 assessment and optimal site cleanup decisions.

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22 Decisions on how and when to use bioavailability to adjust the cleanup goals for a site are  
23 based, at least in part, on a weight-of-evidence approach. In many cases, the necessary  
24 information is lacking, or more often, not known to decision makers. Having access to a useful  
25 database would not only facilitate such decisions, but also go a long way toward identifying  
26 knowledge gaps where additional research is needed. A useful initial effort of any group  
27 brought together to synthesize what we know would be to define the required data elements and  
28 basic structure of the database. The rapidly advancing science of informatics may provide  
29 some new and useful approaches.

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31 3. In almost all research and practice areas related to bioavailability there was agreement  
32 that we do not have adequate models to allow incorporation of what we know into the decision-  
33 making process. We need both conceptual models to help bring the relevant pieces together  
34 and relate them, and numerical models to help predict consequences and outcomes at specific  
35 sites. In both cases, the models need to be far more comprehensive than at present. Existing  
36 models of fate and transport provide a good starting point, but rarely address the health  
37 impacts. The formulation of these models could also reveal knowledge gaps, both generally and  
38 for specific sites. The models should include means to identify and protect vulnerable  
39 populations and can also be used to direct remediation efforts. It may be possible to generate  
40 modular models to deal with specific problem areas (i.e. how soil properties relate to  
41 bioavailability of contaminants) and construct interfaces to other modules that can relate  
42 available materials to exposure (blood levels of contaminant) and disease.

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45 4. There is a pressing need to increase basic research on bioavailability into many areas,  
46 some identified in this report. This research should span the range from environmental  
47 characterization to disease susceptibilities. Basic research leads to new techniques, recognition  
48 of new relationships, and new abilities to predict outcomes. Many synergies and new  
49 approaches evolve when research findings are incorporated into cleanup efforts. Several  
50 examples of cleanup projects were cited where a little extra funding and involvement of  
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1 research scientists could have paid great dividends. For example, large-scale soil sampling  
2 around peoples' homes but not collecting blood samples to allow documentation of exposure is  
3 an opportunity wasted.

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5 5. As with every major conference on contaminants in the environment, the lack of  
6 progress on studies dealing with mixtures was noted. There is still a great need for data on  
7 uptake, toxicology, and disease when humans and ecological receptors are exposed to  
8 mixtures. Likewise, there is little information on how mixtures of chemicals interact in the  
9 environment. This has been a research priority for many years with little real progress. Most of  
10 what is known comes from the wastewater treatment field, but relates mainly to degradation. It  
11 is important to convene a group to discuss useful approaches for research on this difficult  
12 problem. Potential approaches range from the practical side by assessing actual sites with  
13 different chemical mixtures and site properties to assessing health effects data to determine if  
14 there are patterns. Alternatively, an approach similar to NSF's Long Term Ecological Research  
15 sites could identify sites where the physical/chemical environmental matrix would be well  
16 characterized, the contaminants distribution and concentrations are known, and researchers  
17 use the site to answer specific research questions concerning mixtures.

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19 6. Cooperation of the interested parties involved at sites was shown to be far more  
20 effective and efficient than confrontation. Team approaches have always worked better as long  
21 as all parties are working in good faith. Confrontation at a site generally increases both the cost  
22 and the duration of the cleanup. The Hudson River example provided by Drs. Neuhauser and  
23 Sinnott is a useful example of how such efforts work. Mechanisms need to be found to increase  
24 both communication and cooperation.

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26 Related to all of the summary points above is the clear need for cross-disciplinary and cross-  
27 agency interactions, collaborations, and syntheses. It was not clear who among the state and  
28 federal agencies can catalyze this interaction. No single state or federal agency, corporation,  
29 academic institution, or professional group has the resources or expertise to assemble the  
30 database, build the models, or do the synthesis. To be successful, researchers and  
31 practitioners from many fields must come together to share information, produce models and  
32 databases, and develop new regulatory and cleanup approaches. This group should include  
33 representation from at least NIEHS, EPA, NIOSH, ATSDR, SERDP, USGS, NIH, and state  
34 regulatory agencies. It is particularly important that both EPA scientists and field personnel are  
35 included as current communication is not sufficient to ensure the transfer of information. These  
36 interactions need to include communication specialists, environmental chemists, geologists,  
37 microbiologists, toxicologists, physicians, industrial hygienists, and risk assessors.

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39 While bioavailability could be the focus of such an effort, the scope goes far beyond the  
40 consideration of bioavailability adjustment to cleanup goals. It is important to consider the  
41 underlying science and its applications from medicine to site cleanup. There were suggestions  
42 that a professional association of some kind might be able to organize and gather the necessary  
43 people, but it would not have the funds to make it work. Several associations already exist  
44 (Bioavailability Research Group Canada; Bioavailability Research Group Europe; Sediment  
45 Bioavailability Research Alliance), but none appears to have the scope or resources to  
46 approach the synthesis needed. Perhaps an approach analogous to the federal U.S. Global  
47 Change Research Program (USGCRP), with representatives from all the major agencies  
48 included needs to be formed to deal with the myriad aspects of this issue.

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50 Such an effort at synthesis could pay enormous dividends in cost savings, health protection,  
51 and cleanup efficiency. The challenge is how to begin and sustain such an effort. The current

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1 programs within ATSDR and NIOSH represent a meaningful start. Groups within many  
2 agencies are considering the problems of bioavailability, but the effort is neither organized nor  
3 well funded. There was a strong feeling during the final discussion that some organization  
4 needs to be formed to carry on the effort at synthesis that this meeting addressed.  
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## 8 **Research Questions & Comments:**

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10 This section has been organized around specific research areas discussed as part of the  
11 meeting. Within each category the ideas are *not* listed in priority order.

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### 12 **Over-arching**

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- 15 • How do we begin modeling efforts: conceptual or decision?
- 16 • Once a database is built, who will test and improve it?
- 17 • Current models are generally single chemical based. Models for mixtures are needed as  
18 mixed exposures occurs at almost all sites.
- 19 • For which contaminants, sites, and environmental conditions are air exposures significant?
- 20 • What lines of evidence are necessary for using bioavailability to adjust cleanup levels?  
21 Currently, there are guidance documents for some chemicals while none is provided for  
22 most contaminants, particularly organics.
- 23 • If a site has a large number of compounds at varied concentrations, how is one  
24 bioavailability correction factor selected?
- 25 • How can state and federal agencies be encouraged to talk to each other? Even within EPA  
26 different groups do not communicate. This leads to inconsistent guidance or no guidance to  
27 practitioners.
- 28 • How can companies with large amounts of data on chemicals, sites, and health effects be  
29 convinced to share the data?
- 30 • Is there a need to generate benchmarks for research focus? Currently, there is a significant  
31 database for lead. Arsenic would appear to be the next on the list. For organics one or  
32 many PAHs would appear to be the chemicals of choice.
- 33 • How can we apply research on the psychology of understanding and communicating risks to  
34 the development and evaluation of behaviorally realistic and evidence-based risk  
35 communication about bioavailability, perhaps adapted to specific sites and affected  
36 audiences?
- 37 • How can we develop standardized bioavailability assessment protocols for human and  
38 ecological health studies? These could be the outcome of the overall assembly of data and  
39 modeling suggested above.  
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### 41 **Environmental Exposure**

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- 44 • What do we know about the long term fate of currently sequestered materials? Does the  
45 natural diagenesis of soil organic material lead to the release of sequestered materials over  
46 decades as the soil organic materials recycle?
- 47 • What bioavailability endpoints are widely accepted and reliable?
- 48 • What tests need to be developed to relate ecotoxicological tests to humans? These  
49 environmental endpoints may be valuable in a weight-of-evidence approach.

- 1 • Can biological monitoring be used to assess bioavailability? Are there techniques for soil  
2 organisms other than earthworms?  
3 • Is soil pore water the analog for pore water in sediments? In addition to micro-extraction are  
4 there other methods?  
5 • What environmental factors produce variation between pore water or soil/water  
6 concentrations and species uptake?  
7 • Which soil and sediment properties might best predict bioavailability? Which are most  
8 relevant, which are not important? Are we still left with site specific or chemical specific  
9 characterization? Can conceptual models help decide which to use at specific sites?  
10 • How are soil and sediment characteristics changed by sampling (e.g. exposure to air,  
11 mixing) impact the values that are subsequently measured?  
12 • How can we incorporate soil chemistry data into the site assessment as this would help  
13 reach more reasonable decisions?  
14 • How is bioavailability of a chemical affected by other chemicals in a mixture (competitive  
15 effects, synergistic effects, co-metabolic effects)?  
16 • Are there ecological assays that will relate bioassay toxicity to human exposure? Embryonic  
17 Zebrafish? How might they be used?  
18 • Are there sentinel species that can be used for chemical effects and exposure measures?  
19 • Can before and after remediation bioassays be used to guide our site closure?  
20 • What is the value of tests like the Triad Method for assessing bioavailability? Can the  
21 current ecotoxicology bioassay comparison from Texas A&M be used to choose tests for  
22 relating to bioavailability?  
23 • Should we use mesocosm studies to look at multi-species receptor interactions?  
24 • How can a mechanism for government funding of large multi-disciplinary studies be  
25 established? At most specific local or regional sites there are not sufficient funds to mount a  
26 significant research effort. At most sites remediation managers are only and perhaps  
27 rightfully, concerned about their own projects and not how to use the effort to learn  
28 something that might or might not apply to other sites. People managing sites are generally  
29 not researchers and may often not know the questions to ask.

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### **Remediation and Cleanup**

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- 34 • How do we incorporate methods like the SPME into the regulatory process? More methods  
35 are needed that provide a measure of bioavailability.  
36 • Research is needed on methods and approaches that encourage regulatory acceptance of  
37 bioavailability adjustment to cleanup levels. More flexibility is needed in the regulatory goals  
38 for specific sites to allow use of bioavailability and other data to direct cleanup effort.  
39 • We need a suite of tools to assess success of remediation in soil (analog to the sediment  
40 triad).  
41 • How do we balance cleanup costs with knowledge based savings? How expensive does a  
42 cleanup need to be before money is spent to find a cheaper cleanup method? Money spent  
43 on research usually more than pays for itself in reduced cleanup costs, but where is the  
44 point at which it is just cheaper to simply remediate?  
45 • Is there need for a program for post-remediation evaluation of decisions and testing of  
46 whether a site remains clean? For which chemicals is a "rebound effect" relevant? What  
47 are the criteria to use? How should data be reported and to whom? Who pays?  
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2 **Methods Needs and Questions**  
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- 4 • Methods are needed to identify environmental compartments that pose exposure risks (e.g.  
5 SPME for sediments). Measuring concentrations in those compartments would give a way  
6 to direct exposure assessment and cleanup.
- 7 • What are the emerging methods in genomics and proteomics that can be used to assess  
8 exposure and effects?
- 9 • We currently use measurement at limited time points, which may over or underestimate  
10 bioavailable concentrations and bioavailability. Are new methods needed that collect and  
11 analyze data over time?
- 12 • How can database information from other compounds and sites be used to help direct  
13 efforts at specific sites? What are the uncertainties in such an approach?
- 14 • How is uncertainty in the matrix, chemicals, and mixtures at one site used to assist in clean  
15 up decisions at other sites?
- 16 • What biological endpoints that can be assessed routinely, cheaply, and reliably? How do  
17 they get regulatory acceptance?
- 18 • For GI-exposure methods, what are the appropriate parameters to be tested to provide a  
19 better assessment of the result; fasted versus fed; type of diet; chemical speciation in the  
20 sample? The *in vitro* methods look promising, but to be widely applied data are needed on  
21 additional chemicals and properties of the environmental samples that are used.
- 22 • How can host factors (gender, age, nutritional status, disease history) be incorporated into  
23 the *in vitro* toxicity testing?
- 24 • For bioassays, how much replication and what data are needed in addition to the bioassay  
25 results to be most useful?
- 26 • A way to quantify the uncertainty in biological monitoring methods is needed. How do we  
27 mimic matrix effects in bioassays? How do we relate measures of environmental  
28 bioavailability (SPME, etc) to toxicity/bioassays and measures of human uptake?
- 29 • Are there environmental surrogates that can give population variability in uptake of  
30 contaminants?
- 31 • There needs to be generalized agreement on what terms mean and what different assays  
32 actually measure.
- 33 • What are surrogate methods for doing whole animal studies? *In vitro* methods and others  
34 are a good start and will likely be cheaper, faster and easier, but need both scientific and  
35 regulatory guidance on which to use in which circumstances.
- 36 • A pressing need exists for agreement on measurement endpoint. If we cannot clearly define  
37 goal of the measurement, it is hard to develop and assess methods.
- 38 • Models or information synthesis is needed to show how reduction in the response of an  
39 ecological receptor relates to risk of human disease.

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42 **Risk Assessment and Modeling**  
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- 44 • How does one decide on the relevant measures for incorporation into models and risk  
45 assessment? The overall synthesis process suggested above should have this as an initial  
46 priority.
- 47 • Models that consider more than just bioavailability are needed. The models should include  
48 chemical and environmental properties that determine the physical state of the chemical and  
49 the amount that might be available. These models need to be validated in a way that leads  
50 to regulatory acceptance. There may not be one model that works for all sites and

- 1 chemicals, but are there modules within the models that can be used broadly? Transport  
2 terms will be different for metals and organics, as might the exposure routes, but if those  
3 issues are part of the model as modules, modules for specific sites could be devised.
- 4 • What are general principles for use in bioavailability assessment? Do all applications still  
5 need to be site specific or have we learned enough to merely extrapolate? Is there  
6 agreement on some combinations of chemical contaminants and sites where bioavailability  
7 is a concern and others where it is not? Can we use a matrix of chemicals and site  
8 characteristics to direct further testing and what kinds of tests?
  - 9 • Models are needed to assess the physical/chemical state of the contaminant: What should  
10 be included?  $K_{ow}$ , valence states for metals, volatility, soil particle sizes, contaminant  
11 concentration, nature and amount of organic matter. What else?
  - 12 • There is a need to address the variance in "bioavailability correction factors". What is the  
13 source of the variability? Analytical method, sample, matrix, etc.
  - 14 • How do we model human health criteria for incorporation into risk assessment? Is one-in-a-  
15 million protective of special groups near sites?
  - 16 • A conceptual model (discussed above under summary conclusions) that relates matrix  
17 characteristics, routes of potential exposure, receptor pathways, and specific contaminants  
18 would help direct information collection, risk assessment, and cleanup.
  - 19 • Cost/benefit components to risk assessment are needed to evaluate how much to spend  
20 studying cleanup. New models need to incorporate a cost module to help direct information  
21 collection and cleanup technology.
  - 22 • Cost usually drives what data and information we can acquire at a particular site.  
23 With better databases and models it should be possible to better determine what information  
24 needs to be collected and thereby reduce costs.
  - 25 • Better models and databases, particularly if they include cost models, make it easier and  
26 cheaper to do multi-level assessments where initial screening would indicate what data is  
27 needed and what can be achieved for what costs. This approach is part of most risk  
28 analyses and could be expanded and improved.
  - 29 • Is there a line between those chemicals for which bioavailability is a consideration and those  
30 for which it is not? Where do we draw that line?
  - 31 • How is exposure of vulnerable populations modeled?
  - 32 • In a weight-of-evidence approach to decision making, how important is a mechanistic  
33 understanding of each test or indicator?
  - 34 • Who will decide what kind of models we need? A group with broad representation may be  
35 the only way to develop a set of models that are validated and accepted broadly.
  - 36 • Can you extrapolate environmental models to human health?
  - 37 • The right assortment of models will help direct the research to understand what factors are  
38 important to study more.
  - 39 • Improving models requires databases, most of which do not exist or are not in readily  
40 assessable places.
  - 41 • How is risk communication better incorporated into the remediation process? More studies  
42 of the psychology of perception and risk? What can be learned from other communicators-  
43 what can educators, marketing programs, advertising teach that will be helpful in both  
44 convincing the public and establishing trust between agencies and different stakeholders.?
  - 45 • Since it seems that the mechanism is at least as important as the message in  
46 communication, what new approaches can we develop?

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## Human Health

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- 2 • Continued work is needed on development and validation of low cost, rapid *in-vitro* tests for
- 3 dietary uptake. These tests should include incorporation of additional factors to help control
- 4 variability and uncertainty in the result. The tests should include chemicals other than lead.
- 5 • For assessing dietary uptake and how to better use *in vitro* methods, it would be valuable to
- 6 involve nutritional scientists to help determine what factors are important in regulating
- 7 uptake.
- 8 • How does the presence of a chemical on the food surface versus within the food itself
- 9 impact uptake?
- 10 • Do regional and ethnic food preferences, and preparation methods impact the dietary intake
- 11 of specific chemicals? How can this information be incorporated into models?
- 12 • How does genetic and epigenetic difference relate to differences in response to chemicals?
- 13 • More work is needed to expand our knowledge of pollutant impact on vulnerable populations
- 14 including the elderly, those who live very near superfund sites, and those with special
- 15 susceptibility.
- 16 • Because vulnerable populations often have multiple health problems, how can those for
- 17 which bioavailability might be relevant be assessed?
- 18 • More research is needed on pulmonary exposure to Superfund chemicals, particularly
- 19 organics.
- 20 • Better mechanisms to screen health data for indications of particular disease states are
- 21 needed.
- 22 • Develop knowledge about how exposure to chemicals at Superfund sites relates to
- 23 infectious disease, either resulting in infections or making them worse.
- 24 • The medical community needs to be more involved in the study of Superfund sites, both as
- 25 training to help them recognize symptoms of exposure and to involve them in collection of
- 26 data from human populations around superfund sites.
- 27 • It is possible to chose one or only a few chemicals and generate data on bioavailability and
- 28 human disease; lead or arsenic for metals and probably PAH for organics. New genetic
- 29 methods exist that offer endpoints beyond the traditional.
- 30 • How can considerations of ethical and justice issues be incorporated into the knowledge
- 31 assembly and health effects?
- 32 • From a cost perspective is it preferable to study exposure (and bioavailability impacts on
- 33 exposure) or effects in exposed individuals? The assembly of existing data and generation
- 34 of convincing models may provide useful focus for this question.
- 35 • How can QSARs be used to assess human health effects?
- 36 • Assays that relate bioavailability to mesothelioma, chronic inflammatory diseases, and other
- 37 diseases are needed.
- 38 • What are useful biomarkers of exposure to Superfund chemicals and how can they be
- 39 incorporated into models and the risk assessment process?
- 40 • Need better understanding of effects of mixtures on human health or on indicators of human
- 41 health.
- 42 • What are the impacts of multi-generational exposure at low levels? What are reasonable
- 43 methods and endpoints for such studies?
- 44 • What experimental approaches exist for linking ecotoxicological endpoints to human health?
- 45 Is it possible to extrapolate body burden in bioassay species to humans.
- 46 • Is it necessary to settle on one animal model and if so which one? We use the swine model
- 47 but there may be better ones. The assembly of what is known could go a long way toward
- 48 answering many questions about what can be measured, what can be extrapolated and
- 49 what needs to be studied.

