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SUMMARY

Break-out sessions report

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Rationale

To enrich the level of conference interactions and foster dynamic discussions capable of generating new ideas and thoughts for pertinent issue sets, several break-out sessions were convened. In general, break-out sessions provide an opportunity for informal and candid group discussions on a topic relevant to the overall theme of the conference. These sessions are often considered to be the highlight of a conference and also provide a means for every delegate to get involved and present their opinions without hesitancy, a common occurrence associated with more formal plenary sessions.

Questions posed

The delegates were split into two groups. To ensure that each group was equivalent, delegates were carefully assigned to a group based on areas of expertise and background. Three separate break-out sessions were convened during the conference. For each session the two groups received the same question set to initiate discussion. These question sets were:

1. Aerosol particles can be discriminated by size and source. What implications do differences in size and sources have for biological dose and toxicology?

2. What work needs to be done to validate aerosol reduction strategies and promote better health?

3. Can biomarkers of harm and exposure be used to predict aerosol-related harm? If so, how do we validate biomarkers for this purpose?

Synopsis

As with most informal discussions, the conversations meandered in several directions surrounding the central theme for each session. Tangents were explored and sometimes the conversations would wander from one tangent to another. Despite this natural, seemingly chaotic, discussion path the group leaders were able to keep the discussion generally focused on the topic(s) at hand.

This report represents a synthesis of the general group discussions highlighting several topics that were common areas of consensus or need.

Report

Communication (meetings, multidisciplinary, IFSH-type structure, progress toward common language, workshops, fill gaps)

We are in the ordinary position of scientists of having to be content with piecemeal improvements: we can make several things clearer, but we cannot make anything clear.

Frank Plumpton Ramsay

Nothing in science has any value to society if it is not communicated, and scientists are beginning to learn their social obligations.

Anne Roe

If you can't explain something simply, you don't understand it well. Most of the fundamental ideas of science

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are essentially simple, and may, as a rule, be expressed in a language comprehensible to everyone. Everything should be as simple as it can be, yet no simpler

Albert Einstein

Proper communication on many levels is crucial to the dissemination of information and overall progress. Communication must be effective, involve interplay and discussion from diverse groups sharing an interest in a common topic or theme, and must be done using a consistent and more common language set. As indicated in the quotes above, nothing has real value unless it can be communicated and that communication must be as simple as possible so that important information can be clearly understood by the listener and/or reader.

There is significant intrinsic value in developing and utilizing a more common language, building a glossary that everyone can work from. One way to accomplish this is to bring together people from a variety of different disciplines to work on and discuss the same thing.

The elements brought together in this conference seem to be ideal. More meetings of this type need to occur, where people from different groups and expertise can talk candidly with each other. If you look at disciplines represented in this room by the 70 plus attendees, the kind of discussions that have gone on so far, and what we're expecting for the next couple of days, the conference has been reasonable successful in pulling together a substantial diversity of individuals. While it may not represent everybody on the planet that is an expert in each particular field of interest, the conference has certainly accomplished its goal of getting people to talk with people from other backgrounds and expertise, different groups than they are used to talking to. This is a very good thing.

Too often we go to large meetings where once they break out into separate session we end up going with what we know rather than to the topics that we should really be paying attention to and finding out about. In a meeting of upwards of a 5,000 persons, the type of discussions and interactions we have at this conference cannot realistically go on. That is truly unfortunate and results in a lower than optimum level of information exchange.

Despite the success of getting a wide variety of people to this conference there are still some missing parts. We have achieved some success in getting public health officials to attend it remains very hard to get the medical community to come. The medical community needs to be active in such meeting, to become educated and educate the basic scientists.

How do we drive such attendance? Do we need a workshop to identify critical gaps in knowledge and also the promising avenues for research so that individual researchers can have some guidance or is there something else that is important? Monetary support seems to be one key. Our experience in getting epidemiologists, toxicologists, their chemists, and their engineering scientists together is to have lots of money, to have lots of sponsors. Perhaps this is also a way to entice the medical community to participate more in meetings like this one. Perhaps one way to sweeten the pot is to piggyback meeting like this with some of the larger conferences. Attendees could then have two meeting to attend side by side reducing overall travel costs and making a more effective use of time.

Biomarkers

But are we sure of our observational facts? Scientific men are rather fond of saying pontifically that one ought to be quite sure of one's observational facts before embarking on theory. Fortunately those who give this advice do not practice what they preach. Observation and theory get on best when they are mixed together, both helping one another in the pursuit of truth. It is a good rule not to put overmuch confidence in a theory until it has been confirmed by observation. I hope I shall not shock the experimental physicists too much if I add that it is also a good rule not to put overmuch confidence in the observational results that are put forward until they have been confirmed by theory.

Sir Arthur Stanley Eddington

Complexity

The entire field of biomarkers is still in its infancy. Most of us do not have a real appreciation for the complexity of what we are dealing with or a good handle on what we are looking for, that's what makes it so hard. We talk about aerosol exposures, the principle topic of this meeting, and you look at the complexity. Just look at the scanning electron microscopy photos of some of the hard particles. Treating them as simply hard particles underestimates their importance because these particles can be a carrier for a myriad of other things that absorb on the surfaces. You can collect them for analysis with our sophisticated collection devices. But we must also consider that this collection device is also a great carrier. One of the challenges is to appreciate the complexity of what we are dealing with and the biology associated with that complexity.

Need

So we need to ask, do we need biomarkers? If so, what do we need them for and what biomarkers do we want?

The answers depend on what is meant by biomarkers - is it a biomarker of harm, exposure, dose, biological impact, biological effect in people, or susceptibility? Are the biomarkers, biochemical, immunological, genomic, proteomic, morphological or something else?

At a different level, the real issue is in determining whether or not there is truly a health, a public health benefit to the generation, validation, and use of biomarkers. If a benefit is determined and realized, followed by appropriate changes, are those changes beneficial ones or do they result in some other health risk? These are all questions that the scientific, medical, and public health community needs to address and discuss while being cognizant of the complexity and enormous scope of the field.

From the various discussions it seems evident that we need to look at different types of biomarkers and discriminate what types we really want and need, and for what purposes. There is a seemingly endless variety of biomarkers that can be thought of. However, when you look at the varieties carefully, the biomarker purposes seem to overlap and their usefulness becomes fuzzy and complicated by a myriad of confounding factors that affect assays and outcomes.

There is certainly an issue about picking a biomarker that's going useful as the predictive marker because any outcome is going to be influenced by the adaptive response in humans. Biomarkers of exposure seem pretty straightforward. It is relatively simple to figure out what you should be looking for although not necessarily so straightforward to measure it. Biomarkers of effect or biomarkers of harm however are much more challenging because of the adaptive responses. When one considers biomarkers of effect in human clinical or field studies, one must also consider animal, *in vitro*, and perhaps *in situ* experiments. What appear to be missing from consideration are the surrogate assay aspects of the whole risk asset paradigm.

Another aspect of biomarkers of effect in the human population is that we often tend to look at healthy adults. This could skew the results of any study. There ought to be some way of looking at more vulnerable subpopulations to assess and validate biomarkers of effect. Perhaps we need more biomarkers of harm focusing on pathways that would be associated with more vulnerable, more susceptible populations so particular subpopulations could be more easily identified.

Validation

This leads to the question of biomarker validation for this purpose. One could demonstrate up-regulation, down-regulation, or encouragement, but in terms of what does that do from a clinically observable standpoint, that's a tough thing to call because you can do some experiments on human beings but typically you can't do the chronic ones. There are just not practical and they take too long. So maybe validation has to be at different levels - nuclear levels, transcription levels, etc. The ultimate validation might be use in epidemiologic studies if you can wait that long and obtain sufficient information for human benefit.

In reality, if you're really look at harm and at effect (disease outcomes), then we need more bio-indicators of susceptibility. Without such markers vulnerable subpopulations are excluded from studies making it more difficult to link disease outcomes with harm (and even exposure). Unfortunately one might also need specific biomarkers for specific sub-groups to gain the most accurate analysis of harm and effect.

Predictive

Perhaps in order to identify biomarkers that are truly predictive of later event we need to determine what endpoint the biomarker is for and work from there, essentially working backwards from the endpoint. The scientific community needs to determine if it wants to understand pathways, what's really happening, or do we want to predict some endpoint.

There is a scientific conundrum here depending on which part of the scientific community one is from. Many experimental scientists want just the endpoints and predictability. However the medical and pharmaceutical scientists want the pathways to create drugs and treatments to intervene. Typically most clinical biomarkers are something that we use after an observed morphological change or disease. If we really want to effect change, we need to identify biomarkers that are quite a bit upstream, capable of accurately predicting disease long before clinical signs and symptoms are apparent. Such biomarkers need to be specific and useful on a daily basis. All too often, once a biomarker selection is identified from a healthy population, its usefulness seems to wane when applied various stages of unhealthy populations.

Particles

The scientist is a practical man and his are practical (i.e., practically attainable) aims. He does not seek the ultimate but the proximate. He does not speak of the last analysis but rather of the next approximation. His are not those beautiful structures so delicately designed that a single flaw may cause the collapse of the whole. The scientist builds slowly and with a gross but solid kind of masonry. If dissatisfied with any of his work, even if it be near the very foundations, he can replace that part without damage to the remainder. On the

whole he is satisfied with his work, for while science may never be wholly right it certainly is never wholly wrong; and it seems to be improving from decade to decade.

G. N. Lewis

The philosophy of some scientists is to identify substances one by one, identify their harm, determine what the dose response is, reduce the levels in the environment until there is negligible harm, and if there's uncertainty reduce it even further. However, public health officials want to maximize longevity in the population, decrease disease, and so on. Oddly enough those scientific populations are different and they make very different decisions.

When airborne particles are involved in the issue set, it is necessary to differentiate between natural sources and anthropogenic sources, although for straight toxicology it shouldn't make too much of a difference. Regardless, it is still autopsy toxicity that is determined. You may learn something about the natural sources, some may cause harm and some others not. Similarly, some may be carriers of toxic substances while others are less likely to be carriers.

Despite the amount of work already done, we still have fairly crude groupings of particles simply because of the highly complex and heterogeneous nature of them. There are 40,000 plus different minerals and large ranges of different forms of organics. In general, this is why we are stuck with such crude groupings.

A question arose - does size, composition, or source matter? Responses varied dramatically depending on which scientific perspective and background one has. Size was deemed initially important as a determinant of where you put the particle in the biological system. So to some extent, particle size may determine where it ends up in the body and the type of cells it's going to interact with. Unfortunately size alone does not predict biological effect, mechanism of actions, or eventual localization of final effect.

Thus, composition also became an important consideration for toxicity. While some elements may be toxic and others non-toxic, when you consider composition and toxicity you are actually starting to address the host/defense mechanisms with individual components regardless of what they are. Similar to the difficulties with biomarkers, a degree of complexity comes into play here.

However, there was a secondary level where we moved back to a particle effect and the individual composition became less important. This centered on understanding what type of insult we are dealing with. Is the insult a simple impaction of a surface or penetration into the cell? In either case, does the insult trigger solely a local response or is the response more systemic in nature? Is the response an organism response or a stress-type response? In consideration of these factors we shouldn't forget about susceptibility and adaptability. The final take home message is really; (a) it is complex, and (b) we still don't speak a sufficiently common language to clearly define what needs to be done and discuss the options. In this respect it was nice to have a diversity of expertise in one room to discuss these ideas and get different viewpoints.

One aspect that cannot be forgotten is biological response and whether biological dose can be easily addressed. It seems apparent that there is a current phenomenon to concentrate on either physical (or chemical) dose or biological dose. It was determined that scientists need to consider both parts until we can begin to understand the whole story.

The last point to address is what should be the primary research driver, particle toxicity or public health. When considering this query we must keep in mind that toxicologists and public health workers have very different aims. Many scientists might feel that being able to show that removal of a particle from the mix results in an improvement in health, that particle toxicity should be the primary driver. Depending on the composition of the particle this result might be deceiving. A perfect example of this is ammonia. Ammonia is hazardous and it produces ammonium sulfate in the atmosphere. A sub-population of people can be very susceptible to this type of ammonia exposure. However if you remove the ammonia from the atmosphere in a place like Los Angeles, the air becomes more acidic and, therefore, the public health is not ultimately served. The toxicologist feels good but the public does not. The problem is that the right thing for some people is not the right thing for others.

Regulation and risk assessment

"...to ensure that in this new Administration, we base our public policies on the soundest science; that we appoint scientific advisors based on credentials and experience, not on their politics or ideology; and that we are open and honest with the American people about the science behind our decisions."

President Barack Obama

The final discussion topic centered on risk, risk assessment, and regulation. Points of view varied widely in terms of who is currently determining policy and definitions, the regulators or the scientists, and who should be performing these tasks. It seemed clear that no one

really knew if the horse is driving the cart or the cart is driving the horse.

In essence, should the regulators be the one addressing what the risk is and then get the scientists to work? Or do the scientists establish the studies and the data and then the regulators pick up on that? Does the public establish what the risk is and where we need to go with this? Who does it? Following a rather lively discourse the consensus was that nobody really wants to set the precedent.

A question was posed - "What work needs to be done to validate aerosol reduction strategies and promote better health?" Taken from the perspective of risk another question was asked - What is risk?

Essentially there was no consensus on what risk actually is not how it is defined. It can be defined in political terms, or personal terms. Perhaps there are different levels of defining risk. This led to the question, is there an acceptable risk? We couldn't get our arms around that either. How much are we willing to say "this is a risk?" Are we willing to determine a cost-benefit in terms of risk and acceptable risk? Is there ever an acceptable risk? Consensus was that the cost-benefit is what most people are looking for. If science and the regulators stop something and reduce risk, how does that benefit society economically?

The next portion of the discussion centered on regulation. What do we regulate? Do we pick out a component? Do we reduce access to the entire product? The bottom line is that we have to start talking to each other to reach any reasonable consensus. The chemists, toxicologists, epidemiologists, and regulators have to talk to each other. We also must respect personal choices. How far do regulators go in influencing our personal choices? There must be that balance.

How do the regulators know what to regulate? Consensus was that current regulation is driven primarily by politics with only 10-20% based on science. Advocacy and money appear to play a major role in determining policy. However, regulation should be based upon the science, not the scientists nor the regulators telling us what they want.

The challenge for the future in overcoming advocacy positions is that all of these people feel like they have a legitimate stake in the action. Part of the solution is to bring all the stakeholders together in scientific meetings because clearly scientists should be driving the fundamentals that determine public policy. Political risk of public officials whether they're elected or otherwise takes way too large a role in public policy decisions. Too many public officials are afraid to step up and say "You know, this is the right thing to do and I'll stand on that." I guess they're too afraid of either not getting elected or not maintaining their jobs or what have you. The idea of overcoming highly entrenched advocacy positions with science is a tough nut to crack.

Similarly, we as scientists have a responsibility to prod our public officials to make decisions based on fundamental and proven science not on the popular opinion or which way is the wind blowing today. This might be really hard for a politician to do because they argue that the only way they can survive is to get re-elected. As scientists we must remember that we have a responsibility to keep our politicians focused on what are the real issues.

This is a complicated proposition on many levels, just as risk is decided upon at many levels. Somebody has to step forward and regulate, whether it's the regulators, the scientists, the public, the individual, someone has to stand up and say, "There's a problem here and we will assume the risk." Even the scientist can do that as long as they remain cognizant not to invade personal choice and freedom.

According to the quote above the US has embarked on a mission to base policy on sound science rather than politics or ideology. May this mission continue and other nations follow course, inclusive of open communication of ideas and rationale by scientists and regulators alike.