TOXTESTING
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10:00 am

Operator: So all sites are on hold, we are currently checking in additional participants for today's teleconference. We appreciate your patience and please continue to standby. Your call should begin momentarily. Please standby your teleconference is about to begin. Please standby your teleconference is about to begin.

Male Speaker: Good morning welcome to the Toxicity testing press conference hosted by the National Institute Of Health and the US Environmental Protection Agency. This press conference will last for 60 minutes, there will be four primary speakers who will provide brief remarks and then -- and then members of the media will be able to ask questions. To ask questions you can press "* and 1" on your touch-tone phone to enter the queue, you may remove yourself from the queue by pressing the # key. This call will be recorded, transcribed and available on the website of the three sponsoring organizations, the EPA and then from NIH we have two sponsors. The National Human Genome Research Institute and the National Institute of Environmental Health Sciences. Now I will turn the program over to moderator Larry Thompson, Chief of Communications at the National Human Genome Research Institute.

Larry Thompson: Good morning everybody, this is Larry Thompson, on behalf of the National Institute of Health and the US Environmental Protection Agency. I'm pleased to welcome all you news reporters who have joined us for this tele-briefing. I remind you that this is tied to 3 pm embargo today for publication in science magazine. I would like to welcome all the folks up in Boston who are participating at the AAAS meeting to be participating in this tele-briefing, it's great to have you all here. After 2 o'clock there will be background and visuals related to this announcement available on the websites of the respective institutes certainly you can go to genome.gov and you will find all the stuff in our press room as well as at the National Institute of Environmental Health Sciences and at the EPA press room.

So, our expert panel in the speaking order will be Dr. Elias Zerhouni, who is the Director of the National Institute of Health. Dr. Francis Collins, Director of The National Human Genome Research Institute which is part of NIH, Dr. Robert Kavlock, Director of the National Center for Computational Toxicology of the Research & Development at the Environmental Protection Agency, Dr. Samuel Wilson, who is the Acting Director of the National Institute of Environmental Health Sciences and National Toxicology Program which is also part of NIH and then we will have a bunch of additional experts from the agencies who will assist in answering your questions especially the technical ones, so we have Dr. Christopher Austin, who is the Director of the NIH Chemical Genomics Center, Dr. John Bucher, who is the associate director of the National Toxicology Program, Dr. Raymond Tice, the Acting Branch Chief of Bimolecular Screening Branch at the National Toxicology Program. So now let me introduce Dr. Zerhouni who has some brief opening remark. Dr. Zerhouni.

Dr. Elias Zerhouni: Oh thanks Larry, thank you for joining us. I think this is a very exciting time and today we are seeing the birth of what I would consider a new approach to a crucial problem in public health arising from the NIH roadmap for medical research. It is obvious that we have needed for a long time a way of exploring toxic -- the toxicology space if you will in systems other than animal systems. And the roadmap (unintelligible) presented five years ago was really a space to -- to explore and pilot new approaches and then it wasn't really a design to initially think about toxicology but when we envision these projects and collaborations, the idea was that with a current need for larger scale, more complex, larger scope experiments that are bigger than what any single scientist or even institutes can support. We thought that this would lead to scientific projects that at that time could not be predicted and it's clear that this announcement today is showing a outcome that was completely unexpected three four years ago.

We did intend the roadmap to be strategic to form high risk projects that had potentially big pay off and we selected the molecular libraries and imaging components at the time and when we did it, we envisioned creating a library of chemicals that could be used by individual scientists to probe the complexity of biological systems. To help us understand and bettering health and disease and hopefully screen for compound that might only provide treatments and provide clues more importantly to the complexity of the biology underlying the disease. We are just clearly early in the development of this but already we are seeing dramatic progress in the sense that we have now new technologies that has been scaled up to the extent that you can in fact envision the ability now to screen for toxicity in a completely new way.

We have the ten high throughput screening centers operating within the network from New York to Pennsylvania and Philadelphia to Emory University in Atlanta, the Scripps Research Institute and all the data that is produced is made public into a public database called (pubcam). This is the fundamental tenant I think of the NIH strategy here including the announcement today in collaboration with EPA, NIEHS and NHERI. We think it is very important for the entire public worldwide to have access to these very precious experimental results so that more insight can be gained. The systems, the research were aimed at developing new treatment for example, next week there will be an announcement about a breakthrough for the first time in 45 years in the treatment of Schistosomiasis, a rare disease that would not be of interest to -- in terms of financial interest or Gaucher's disease which is also in the work.

But I think today what we are really wanting to report to you is this remarkably unique collaboration, one that I could not have foreseen when I saw the road map initiatives with my colleague Dr. Francis Collins and Dr. Tom Insel and this is in some ways an example of how we can go forward when we see technologies arise from completely -- completely unexpected corners of the field of science and have an application which I personally did not envision just a few years ago. So with that I will, I think I will turn it over to my colleague Dr. Francis Collins who would -- who will brief you more in this collaboration.

Dr. Francis Collins: Thanks Elias and good morning to all of you. The research collaboration we are announcing today really has the potential to revolutionize the way that toxic chemicals are identified. As you know, historically such toxicity has often been determined by injecting

chemicals into laboratory animals, watching to see if the animals get picked and then looking at their tissues under the microscope and though that approach has given us valuable information, it is clearly quite expensive, it is time consuming, it uses animals in large numbers and it doesn't always predict which chemicals would be harmful to humans, the correlation is not as precise as we would like. So what's being proposed today and outlined in a paper being published tomorrow in science magazine to which your attention is drawn and again note the embargo about this that was mentioned by Larry Thompson, is to bring together the skills of three established scientific organizations from two different federal agencies into a whole of that is certainly stronger than any other parts alone.

So what are these three components, first of all you heard already from Elias about the National Institutes of Health roadmap project in small molecules as a chemical genomic center at NIH, the NCGC is the component of today's announcement that brings the high throughput screening technology to the table. Its staff are led by Chris Austin and many other really talented colleagues knows how to test millions of compounds quickly and cost effectively. The scientist at the National Toxicology Program part of the National Institutes of Environmental Health scientists know more about chemical toxicity than just about any other group on earth, and decades work with animal research experience to guide this project. And the environmental protected agencies office of research and development is filled with real experts in chemical informatics whose computational skills will put all this data together compared to the historical animal data and draw inferences about what kind of new approaches we could take for high throughput identification of toxicities associated with compounds that haven't previously been tested.

So together this information will help the NTP and the EPA do their job to protect all of us and the environment from harmful chemicals. I should be clear however, that despite the promise, this collaboration is still a research effort, there is a lot we have to learn and that's why a Memorandum Of Understanding has been signed for a five year project here to research, develop and validate these new and innovative toxicity testing methods. We suspect although this is for five years that this collaboration will probably last many years into the future. The idea being to usher toxicology screening really into the 21st century providing the kind of capacity which was envisioned in a recent report by the national research council that cost from the development of justice kind of systematic screening systems that could eventually take the place on animal based designation of chemical toxicity.

Now, let me give you some details about how this will work. The NIH Chemical Genomic Center provides this pubic sector capability of industrial scale technologies for high throughput screening and chemistry. The center is already highly capable of identifying small molecules yet to be used as chemical folks to study the functions of gene cells and biochemical pathways. It's even possible that some of these chemicals like the one that Elias mentioned for Schistosomiasis may end up being new medications for rare diseases, which is a great health provider. But of course there is a flip side to this if you can use the same screening system to identify beneficial compounds you may also apply the same technologies to see whether certain compounds have toxic effects. It is basically the same strategy but with a different output we can use the robotic plating of Lincoln, quantitative high throughput screening, which is really amazing to see if you have the

chance to come and visit this center you would be I think quite taken by the robotic capabilities that now exist here.

So, because the NCGC can test so many chemicals at one time it can also test one chemical at 15 different concentrations, which is really important for toxicology. You want to know not just is this compound something that might be harmful but at what concentrations would that harm occur because almost anything if given in a very high concentration could be toxic and you want to know what those dose response looks like and this is where NCGC is extremely experienced and makes it a wonderful partner for this enterprise.

Finally, let me say that the scientist involved in this collaborations didn't just decide to get together this morning to make this announcement and they have been working with each other for quite a while testing their ideas already NCGC have analyzed something like 2800 compounds including pesticides and industrial chemicals and in fact there is a publication in the journal environmental health perspective reporting the result of about 1400 compounds that were supplied by the national toxicology program and were tested against 13 different types of cells to see what their consequences would be over this range of concentrations. So this is an early publication of what will undoubtedly be a very large output from this collaborative effort.

So finally I would like to say the merit of this Chemical Genomic Center Technology with the experts in us collaborating institutions at the NTP and the EPA is a really powerful and promising advance and I think it is both good science and it's a wonderful example of how federal agencies seeing the real opportunity can get together and do

something collaboratively to try to benefit the public. So let me now turn this over to my good colleague from the EPA Bob Kavlock, Bob.

Dr. Robert Kavlock: Let me first express my regret to Dr. George Gray Assistant Administrator for Research and Development of EPA who was scheduled to participate in this briefing but he was called to testify to Congress during the same time period. EPA and regulatory agencies around the world are facing an increasing gap between the number of chemicals for which we need to access toxicity and the ability of traditional lab based animal studies supply that needed information. EPA recognize the opportunities afforded by advances in molecular biology and computer science, provide faster and more effective chemical assessment procedures, when it established The National Center For Computational Toxicology three years ago. The NCCT has lead within the office of research and development to bringing these new tools to environmental protection. A research is working closely with its clients in the regulatory offices to provide solutions on how to determine which chemicals along with the candidates for which they are responsible are the most important for us to study.

The approaches can also be used to reaffirm or modify existing approaches such as the category approach to chemicals under the high production volume chemical program. Our ToxTest Program launched in 2007 is nearing completion of its first phase of development and it's evaluating the effects of more than 300 chemicals and nearly 400 different in vitro assays to develop predictions of the outcomes of test in traditional animal model. We expect to be in the next phase of extending and validating the predictions by the end of this year. The ability to interact with the National Toxicology Program

and the NIH Chemical Genomics Center will allow us to move faster by uniting complementary expertise of the three partners.

Already we are working together to coordinate the chemicals we are studying, the toxicity pathways that will be studied, the data we are obtaining and the methods to interpret and understand that information. The international community is also interested in this issue as evidenced by the establishment of a working group by molecular screening under the organization of the -- on the cooperation and development for which EPA is current lead. We welcome additional partners to join us as we move to integrate the more efficient and effective methods in the assessment of human and ecological risk of chemicals and we look forward to the questions from the media.

Larry Thompson: Thank you. Okay. And Dr. Wilson from the National Institute of Environmental Health Sciences, please go ahead.

Dr. Samuel Wilson Larry, thank you very much. We, at the NIEHS and the NTP are very excited to participate in this collaboration with the EPA and NCGC. The power of the collaboration is bringing together new strategies and technologies to address important needs in toxicology. The collaboration comes at a time when the biochemical pathways underlying responses to toxicants are becoming well understood. Making use of this information within the collaboration will lead to a new toxicology paradigm that will transform toxicology and toxicity testing and provide a path towards better protection of public health as it relates to chemicals in the environment.

Now, the National Toxicology Program has been committed to characterizing the toxicity of chemicals through its bioassay program

into the development of methods to improve our ability to identify hazards in the environment. As an interagency program, the NTP collaborates with many groups to develop the information needed for regulatory decision-making. Our commitment to the NTP bioassay and to meeting public health needs of regulatory agencies will continue. The NTP released its vision and roadmap for the 21st century in 2004. And this included initiatives to integrate high throughput screening of chemicals into the NTP testing program. The NTP's expertise in toxicology and its large database of chemical effects in animals will play critical roles in evaluating the High Throughput Testing process that we are announcing today.

We recognize that full implementation of a new toxicology paradigm will require substantial effort over many years, but ultimately will allow us to generate data more relevant to humans as Dr. Collins said earlier and to reduce animal use in toxicity testing. In closing, we look forward to working with the EPA and the NCGC in this collaborative effort that will greatly benefit public health.

Larry Thompson: Great. Thank you very much Dr. Wilson. So, what we would like to do now is open this up for your questions. So, I would ask you to you know, join the queue as instructed by our operator and please identify yourself and your news organization so we know who we are talking to. I remind my colleagues that when -- you can't see our faces. So, you know, tell -- say who you are when you start your answer so that reporters will quote the right person and we have some of our experts also gathered here to help answer any of your really technical questions. So, why don't we start with the first question please?

Operator: Our first question will go from (Pat Lucido), your line is open.

Pat Lucido: Hi. Clarification and then, a question. Dr. Kavlock, could you repeat the number of in vitro assays that you have said were part of the phase I?

Dr. Robert Kavlock: This is Bob Kavlock. Within phase I, depending on actually how you count them, it's somewhere between 350 and 400 assays we are having right now. We have added a few additional partners over the last few months. So, the number has grown.

Pat Lucido: And then, my second question to whomever would be, there is great interest in alternative test in the nano world. Is there a component of this that will help determine whether these alternative tests can also predict toxicities for intentionally engineered nanomaterials?

Dr. Robert Kavlock: This is Bob Kavlock from EPA. We certainly think some of these technologies are going to be used for looking at nanomaterials and in the next phase of our ToxTest program. We plan to test about 10 or so chemicals for which we have some animal data already. But we are optimistic it will be useful for them.

Pat Lucido: And how many years do you think it will take before you are confident with the predictions for regular chemicals?

Dr. Francis Collins: This is Francis Collins. Let me say this, this is after all being announced as a research enterprise and we need to figure out exactly what the correlations are going to be between the results of animal testing and this new High Throughput approach which will involve both cellular assays and in some instances, assays of model organisms like zebrafish for instance. Of course, we have a wonderful legacy

database of information where you know what the answer is and that's going to have to be used then, to tune the system to try to assess which of these new assays are most predictive of the results if these toxicities are to be believed in humans. But exactly the time over which it will take to develop that is -- well, that's why it's research. I think we did have a pretty tough time predicting exactly what that pathway is going to look like. I think the news today is that we do now have the pieces in place to be able to ask that question and answer it effectively.

Pat Lucido: Thank you.

Larry Thompson: One more response by Dr. Wilson and then, we will move to the next question. Dr. Wilson?

Dr. Samuel Wilson Yeah. I think the answer to your question actually would depend on the type of chemical or the type of exposure under investigation so that in some cases, the pathways are well enough worked out with attendant models in self-cultured systems and animal systems so that we could very rapidly do the cross species and cross system validation necessary to document the information obtained through the high throughput approach. So, we think that in the relatively short-term that is in the next two or three years, there will be some examples where the high throughput information can inform in a very meaningful way as to the priority settings or cell model testing and then, for use of animal models to confirm the information that we glean from these other approaches. Let me also ask my colleague in the National Toxicology Program, John Bucher to comment on this point.

Dr. John Bucher: Okay. This is John Booker. We really look upon this as an iterative process because we are going to be learning so much in the very beginning, that's going to -- that's going to really guide us in the further development of this program. Just to predict exactly how long it's going to take at this stage it's very, very difficult. But the process is going to involve stages of convincing the thought first and the scientific community at large that the prediction and the output of these assays are really making sense in the sense of biological term. Then, there is going to be the stage of convincing the scientific community at large that this is the right approach to take and then, finally, the regulatory communities they are going to have to be involved in the these steps from the very beginning and probing on with us as we go.

Larry Thompson: Okay. Go on to the next question please.

Operator: We will go next to the site of Maggie Fox from Reuters. Your line is open.

Maggie Fox: Hi. I am sorry, you have got -- you have got me now and I just wanted to say, can you guys start all over again and do this in cocktail party language because I am not clear exactly what it is you are saying. Are you saying you are shifting over to non-animal testing and you think it's going to be more accurate? I apologize, but I need words of one syllable.

Dr. Francis Collins: Hi Maggie, this is Francis Collins and I guess I am the elected cocktail party participant here. So, let me see if I could try this again. I am sorry if it's been a little too technical. Basically, we really need to know for all kinds of good reasons whether a particular compound has the potential of doing harm to human beings. We would all agree with

that, right? That is the science of toxicology. The way in which that has been done over many decades has depended heavily upon the use of animals where you basically decide okay, I am going to take a particular animal species or more than one and apply this compound at a variety of concentration and I am going to look to see does the animal get sick. And if it looks like it's getting sick or sometimes even if it isn't, you then, look at the tissues of the animal and try to determine what exactly was the damage that was done here, what organ system was affected.

This has been our mainstay for trying to make predictions about human toxicology, but I don't think anybody would say, we are totally happy with it. It's slow, it's expensive and its precise predictive ability has often-turned out not to be as good as we would want. There are differences between species. We are not rats and we are not even other primates and so that desire here is to try to see if we could best. Now there has been much discussion including a recent report by the National Research Council about moving toxicology testing into a new 21st century kind of era where we take advantage of a lot of the things we can now do based on technologies that come from other direction. Many of them I will happily tell you from the genome project, that make it feasible has to begin to imagine a toxicology in a totally new way.

After all ultimately what you are looking for is does this compound do damage to cells, so could we in fact instead of looking at a whole animal as our first line of analysis look at individual cells from different organs of different animals with different concentrations of the compound and taking advantage also of what we are learning about the fact that you know microbiology is coming along. We have a better sense about pathways involved in the cell that we are used to and you

might be able to begin to make inferences about what's going on by tapping into that information about so called systems biology.

So the proposal here Maggie and it is a proposal which is now going to be tested in a rigorous research environment is that at least in some instances in the longer term we might be able to do a better job of predicting toxicity by using these high throughput cell based assays where you basically try the compound in a laboratory situation on cells growing in a little timey well of a plate and would in that situation be able to assess is it hurt -- is it likely to hurt the liver or the kidney or the brain of an individual because you collected that data in a high throughput, low cost and much less low risk, much more amendable risk situation than what we have currently done.

But we don't know if that is going to be as good as we would like and so hence this purpose of this collaboration is to test this out particularly now using situations where we know the answer because we have a list of compounds that we know do create human toxicities. If we didn't already know those answers, could we actually develop a system that would have predicted them accurately? That's kind of where we are trying to go you got to tune the whole process before you can just assume that it's going to have that predictive power that we want. Now does that help or do you want to push back with the question or two?

Maggie Fox: No, that -- that helps. So you are not going to use human cells with any of these animal cells?

Dr. Francis Collins: Oh no we are definitely using human cells.

Maggie Fox: Oh I'm sorry.

Dr. Francis Collins: And again we have access to a lot of different human cells growing in culture these days and probably the goal here will be to test out as many different ones as possible to see which of those is the most predictive of what we really want to know which is toxicity to human beings.

Maggie Fox: Thank you.

Larry Thompson: Okay. One more short quick answer from Dr Wilson before we move on?

Dr. Samuel Wilson: Yes, I think I will take a crack at this question Maggie also this is Sam Wilson. In the toxicology community with known for a long time that we need to improve this throughput of our testing to able to test many thousands of compounds but today we are not able to test because we simply don't have sufficient throughput. Secondly, the cross species extrapolation of information that we gain from animal model studies to humans is not always as efficient and precise as it should be. So we have a big recognized need in the field of toxicology that have more precise ways of predicting human toxicities.

This collaboration we are announcing today really is a milestone because just for the first time it gives us the power, the research power and the opportunity to apply a whole new generation of approaches to this question of toxicity. Now as I said in my comments earlier in the vision or strategic plans with the National Toxicology Program several years ago, we recognized the opportunity or the need for taking this stuff. But today is the first time that we have actually formalized the collaboration at least here in the United States that will give us a shot

at achieving this vision that we laid out in our strategic plan and we have been talking about today.

Dr. Elias Zerhouni: Cool. I have been -- I have been to many cocktail --.

Male Speaker: This is Dr. Zerhouni?

Dr. Elias Zerhouni: Yeah, this is Dr. Zerhouni. I think you are posing the fundamental question, I think what you are saying here is the fact that as a society we need to be able to test thousands of compounds in thousands of condition, in much -- in a much faster rate than we did before. These technologies which have come up through genomics technology, chemical genomic technologies which we have really developed to screen for example three hundred thousand potential drugs in less than the couple of days. This where -- this would have taken three years, five years ago. And because of the scaling up the natural idea, that I think is being proposed here is to move the 20th century paradigm of testing of one component at a time in many animals, to going to the 21st century paradigm tests five -- 10,000 compounds against 5, 10, 20,000 conditions in cells that are very specific to human toxicology.

And because of doing that what we hope to do is accumulate enough knowledge based on what we already know to crosswalk from the 20th century methods if you will, crosswalk reliably in a validated way, to what we would call high throughput 21st century toxicology. And this is what this whole project is about, this is why I think we are excited about it is to move forward at a pace and rate which will be consistent with the toxicology risk that we see in human society including new compounds.

Larry Thompson: So I would observe that is Larry Thompson, I'm going to observe that we have about 20 minutes with our friends in both in Boston and then -- how can you get out of the newsroom? So when we go to a question in Boston first and let's -- let me ask one of colleagues to keep your answers as short as we can, so we can get as many reported questions as possible. So we got a question two from Boston and then go back to the general queue.

Male Speaker: We do have couple of question from Boston and I will ask the reporter to give the name and affiliation.

Male Speaker: Okay, thank you.

Rachel Aronberg: My name is Rachel Aronberg, I'm with Times News and I have a couple of questions. One is by high throughput, you just mean a lot at once and if you could also please just take through an example of okay there is a chemical you want to test. You have your little dish of cells, how they are doing various concentrations, how frequently might you check on it, how do you then determine if damage has been done and also how are you prioritizing which compounds to be first?

Larry Thompson: So okay, Dr. Austin please introduce yourself.

Dr. Christopher Austin: It's Chris Austin; I'm the Director of the NIH Chemical Genomics Center. It's great question. How this actually works is we take a dish that’s about 3.5 -- 3 inches by five inches that contains 1536 different little wells in it. Those little (wells) are a fraction of a millimeter across and we put the same cells in every one of those 1536 little -- little containers that’s within that dish, within that tray. Then we

take 1536 different chemicals and we put them on top of those cells, and we do that on multiple different trays so put traces of cell and the compounds are all the same in those 1536 little -- little containers in that tray, but their concentration vary over about a 100,000 for concentration range, so very -- very wide concentrations.

And there are variety of ways to look at how cells are being affected of in technical terms and what one does is it comes down to a detections of white of one sort or another, fundamentally which ones looking at is in the most growth example is if you -- if you ask the machine, if you ask the reader to tell you how many cells are left in a plate, if you killed off half the cells, if there are half as many cells in one little well of that 1536 well tray then in the -- in the container that means that you killed off half the cells of the compounds was -- was toxic, that's the most growth example.

In other examples you can look at specific pathways by marking those pathways with markers that are used to detect whether a particular say the pathway is increasing an activity or decreasing activity. It's rather routine in -- in a Chemical Genomics and drug discovery world and we can use this for toxicity testing too. As far as, how long we waste is one of the things that we haven't in the experiment but we tested different concentrations but we also tested the same concentration at a different times. And so sometimes we will wait five minutes, some times we will wait one day, some times we will wait two days, some times even longer than that. And of course the effects that you see are some times different depending on how toxic a compound is.

So the answer is that in order to get the answers you want you have to do all the conditions, all the different concentrations all the time and

that's why we need to have such a high throughput system. I should say that we -- we talked about this in theoretical terms up until now, but you have mentioned before that we have been working on this for about the last two years in and -- have shown which is what allows us to announce this today. Technically the process works. We know we can generate reliable data, and so that's why we feel like we are able to announce this today, to scale up to larger numbers of compounds somewhere between 10,000 and perhaps a 100,000 compounds, its several hundred different assay conditions.

Larry Thompson: Has Dr. Bucher also to make a comment from NIEHS?

Dr. John Bucher: Yes. I'm going to address the issues related to the how you set priorities and what this, we are going to be going forward testing. And also give you some perspective of the scale of the problem. NTP has been in operation about 30 years now and we have tested in very great detail about 2500 chemical. And that in narration to the chemical, the numbers of chemicals we are talking about testing here is a very, very small numbers. But we will start with those 2500 chemicals as our first priority, because we have a very rich database of information on those chemicals and we can compare the output from these cell based assay in terms of whether these chemicals cause cancer, reproductive and developmental effects, neurological effects, immuno toxic effects and various other kinds of toxicity

Larry Thompson: Doctor, other question from Boston.

Male Speaker: We have two more questions form Boston; we will try to make them quick.

Male Speaker: Thank you. Please proceed identify yourself.

(Helen Briggs): Hi, Helen Briggs from the BBC. Could I just press you a little more on the time frame, and also if this becomes a reality how many animals and I could save a year?

Male Speaker: Do we have anybody actually done that kind of -- I don't know if anybody done that kind of a calculation yet have we?

Male Speaker: So this, I think would be sufficiently hypothetical that it's probably not wise on our part to try to give a specific time frame or prediction about the change in animal testing that will result, I hope you understand what's being talked about here is an assessment of a brand new approach to try to do high throughput screenings, the toxicity testing, a very large number of compounds and exactly with the trajectory is of that science going forward is not really possible for us to say at the moment. I think having said that, its fair to say the organizations involved in this are not interested in going slow race. We are interested in pointing this agenda as fast as we can and certainly one of the hopes for outcomes of this would be a reduction as soon as possible and the number of animals that are necessary for being tested.

Dr. Robert Kavlock: This is Dr. Kavlock at EPA and I would echo the urgency that we that we work with this, and I know the groups are planning a meeting in March to begin the layout at a timeline for a actual working through this a Memo of understanding.

Dr. Elias Zerhouni: This is Dr. Zerhouni. I would like to point out to everyone that, the work has already started. In other words this isn't theoretical if you go

to the issues the underlying issue of November 22nd 2007 of environmental health perspective, as you will find the work that has been piloted really, there's been a pilot behind this whole proposal of testing more than 2800 NTP and EPA compounds, which are -- which where tested or with over 50 biochemical's in cell based assays. I think if you -- if you went to that paper, you would see exactly the format as what needs to be scaled up but as far as starting and testing and road testing the concepts that's already been done.

Larry Thompson: Next question.

Dr. Elias Zerhouni: (Unintelligible) please.

Phil McKenna: Hi this is (Phil McKenna) from New Scientist. I'm wondering if you could go over again, how much faster compared to your animal test, or and if this works, are there applications outside of toxicology and again what was the regulatory approval that would be needed for this?

Dr. Christopher Austin: Okay, so I will give you, this is Chris Austin again. I will give you a sense of the timing. An example we frequently use is that to test the 100,000 compounds in 15 different concentrations takes us two days. We calculated -- we would take a person, if you were going to do the same thing, a one person would have to work eight hours a day, seven days a week for six months, to get that -- to get that done and we do it in two days. And so it's -- it's much -- much faster. As far as doing it in animals it would be, to test a 100,000 compounds in animals, it would be physically impossible.

Male Speaker: Yes. Well, we know this will put about, it's been 2500 over 30 years.

Dr. Christopher Austin: Right.

Male Speaker: And to do 2500 we do 2515 concentrations in a single afternoon. So single afternoon versus 30 years.

Male Speaker: Hey you might want to mention --.

Male Speaker: Yeah.

Male Speaker: -- the footage that's available, people want to see what the system looks like.

Male Speaker: So yeah we (unintelligible).gov at 2 o'clock today will post on our website, (unintelligible) footage of the high throughput screen system, it's a series of robots and incubators and (cara cells) that have these questions of chemicals in their chemical library. It's chemical stuff to look at, so you can watch it right on the website in Flash. And for broadcasters, you will be able to download quick time movies that are in full resolution that can be imported directly into a non-linear video editor for using a broadcast piece. There is about 15 or 20 clips, I can't remember how much and you know, couple of sounds bites from Dr. Austin, who is the director of the center. So if you want to just see this thing and see what their -- the system that we are talking about, should be able look at it in about two hours. Next one more question or let's get back to the regular queue, we are done in Boston, right?

Male Speaker: Yes, that’s it for Boston.

Larry Thompson: Okay.

Dr. Robert Kavlock: This is Dr. Kavlock from EPA, I have -- the last question, I mean so we didn't get to was the application outside Toxicity Testing.

Male Speaker: Okay.

Dr. Robert Kavlock: These actually are inside Toxicity Testing, but you can think about applying this to mixtures for instance, which is a very difficult issue to deal within toxicology. You can deal with lot differences of chemicals and understand whether there is differences in contaminants between them. Or you can develop high throughput screening assays to look for genetic susceptibilities that might be useful for finding susceptible blood populations. And then in terms of regulatory adjustments, I think that depends on the use in terms of screening and prioritization, those kind of acceptances I think would come quite early as we just identified those chemicals that are most important to study. If we talk about actually replacing animal test with these in vitros that will be a much longer route and require perhaps even different legislations that we are dealing with right now.

Dr. Christopher Austin: Yeah this is Chris Austin and just very briefly that one of the major points about this just to reiterate it, but if it did use a do use technology. In fact this technology was developed and we use it everyday to develop chemical probes, understand the genome and starting points for development of new therapeutics particularly for rare and often disease that are of interest NIH. The same technology essentially, with some important modifications that is used within pharma. And so we have taken that technology and applied it to a completely different use. So already, it's a multi use and do use technology that has been developed elsewhere and applied to a new application.

Male Speaker: Lets go to our next question please.

Larry Thompson: We will go next to Lauren (Neargard) from the Associated Press, your line is open.

Lauren: Hi I would like to also this in a little more global context. My understanding is the European union is about to enact a ban on animal testing of cosmetics. And it sounds like from what you are telling us here you know, you all are at the very beginning of this in terms of how reproducible using this instead would be. So if you could just comment a little bit on what's going on globally and how your work will apply to that? And then I would love some specific examples of chemicals today that you know; the animal testing has not been able to answer the certain questions that this perhaps could.

Male Speaker: Okay. Dr. Wilson will go first and Dr. Kavlock to answer and Lauren keep this -- keep this follow up.

Dr. Robert Kavlock: Yes, so concerning the first portion of your question about some of the trends and thinking in that E use. It's true that they are considering the approach of discontinuing animal testing. And this is broader than the cosmetics industry; it actually extends to the entire chemical industry and the -initiatives under the acronym reach. Now they are planning and research on alternate approaches other than animal testing or how to assess hazard and toxicity is in a very, very early stage. Probably, even earlier by a considerable margin than our research here in the United States. The alternate approach that we are talking about here today really is a step in the right direction towards a more robust method or technology for assessing a whole

range of chemicals as we have said. But I think that our approach here in the US is actually a little more mature than there is in the EU. Let me ask now John Bucher to say a few words about a specific example of limitations that we have with animal testing.

John Bucher: Well, in many cases we say that distinguish the response of animals and humans are related to the rates of metabolism, that the various organism have for various chemicals. So in one case, you will have animals strains and species that are particularly sensitive, particularly chemicals and in another cases close same chemicals don't seem to have the same effect in human. There -- and some historical instances, where humans had proven to be more sensitive than the animals to substance (unintelligible) in earlier examples, a long time ago. Those are classic examples that's made us really be aware that the animals are not always giving us the right answer, but then we have to obviously use all the information that we can get from all kinds of different systems to generate data that are going to be predictive of human health.

Male Speaker: And Dr. Kavlock, we asked you to sort of address the international regulatory part, Dr. Kavlock you still with us?

Dr. Robert Kavlock: Yes, I am. I'm sorry, we just were on mute. It's Dr. Kavlock at EPA. This is why we are working with the organization of economic and cooperation and development in Paris to bring an international perspective to this. We have introduced this molecular screening initiated to them about two years ago. And there is now a working group form that has representatives from Canada, from Japan, from Netherlands, from England, from Germany and a number of other countries that are meeting to -- begin to understand how we can bring

this kind of technology to the international field. We have also had discussions with European chemical agency and with European commission in Brazil about supporting research in Europe that would compliment the kind of research that we are doing here in the United States and those discussions are continuing.

Larry Thompson: True, Dr. Zerhouni?

Dr. Elias Zerhouni: This is Dr. Zerhouni, I would like to point out however Lauren, it's very important to also state you cannot abandon animal testing overnight. As I said there is a very important crosswalk that needs to occur between animal base technologies versus non-animal based technologies and at this point, I don't think one could say, and you could validate the new technologies and abandon roughly animal testing, it will have to be intertwined for a years until we fully understand the scope and scale of the problem.

Larry Thompson: We will go to the next question please.

Male Speaker: We will go next to the site of Elizabeth Weis from USA today, your line is open.

Elizabeth Weis: Yeah, I wanted to ask if you could go back to the beginning because you were -- it sounded as if this was a (unintelligible) outcome of research that you hadn't expected to lead to this. And again, I will ask for the -- the words of one syllable will cost no party discussion of exactly how that happened?

Dr. Elias Zerhouni: This is Dr. Zerhouni again. I think what the intent was initially -- was really to be able to analyze biological pathways in health and

disease with the purpose of developing therapeutics or diagnostics. We really did not see the paradigm of looking at this approach at that time for toxicology study. However, as we progress what was really amazing is the fact that A, we realize that we could in fact test many hundreds of thousands of compounds in the space of a week for a therapeutic purposes, we had shown that this could be done reliably at different dozes which is what the work of Chris Austin was and all of the sudden Eureka, a moment occur, because you had a conjunction of interest here.

The national resource council was looking at the issue of toxicology, NIEHS was looking at the issue of scaling up our ability to study many compounds as you know, globalization is leading to the production of many, many hundreds of thousands of compound and one plus one became three. And we can do logic on his head and instead of testing compounds with therapeutic practices, what about testing them, so they are potential to disrupt -- disrupt normal physiology in an analytical way that would be completely different. That was the unexpected nature, because you really don't -- cannot predict in online where the breakthroughs are going to be, because you see progress in multiple fronts, which all of a sudden create a new horizon.

Female Speaker: And about when would you say that happen that was two years ago?

Dr. Elias Zerhouni: I would say three years ago. Dr. Bucher and Dr. Kavlock?

Male Speaker: Yeah.

Dr. Francis Collins: This is Francis Collins, and isn't this actually a wonderful example of what you hope will happen in science that you develop a technology for one purpose with the hope that it's going to work there and it starts to work and then you realize, goodness we could take this approach and apply, it's a totally different problem that we haven't initially thought of. This happened over and over again, I mean who thought when the (unintelligible) was being put up to try to handle a small amount of data that needed to go from one place to the other. I was in the defense industry, then we would end up with the World Wide Web and the Internet knowledge that's been off from it. Again I think that's what we are trying to do, by bringing together technologies and scientific needs, that you could not predict it, even though few short years ago would fit together realizing that they do, and then trying to put together the appropriate framework, to push the science forward as quickly as possible.

Female Speaker: Thanks so much.

Larry Thompson: Next question.

Operator: We'll go next to site of Robert Stevenson from International Scientific Communications, your line is open.

Robert Stevenson: Thank you. I'm struck by the apparent parallel wasn't be clean, the Human Genome project which involved competition between the private sector and the public sector and Dr. Collins was involved in that. And what we are doing here, I mean the drug companies are Novartis for instance, is 350 screens done in the last three years generating screens against a million compound and again in the afternoon or so. It just seems like we are reinventing the real here, this

information is you know, it's already been collected by society and being processed daily, I just -- I'm really not so impressed.

Dr. Francis Collins: Well, I'm sorry this is Francis Collins, let me try to impress you, or clarify this a little bit, I think you are missing up a couple of things here. What Novartis is doing with their screens, which we all celebrate and hope they will do more and fine more wonderful jobs for common disease is to look for compounds that have positive effects on a potential disease state. What we are talking about here is to turn that around to try to identify compounds that maybe toxic in the environment, the air, the water, this is not something that Novartis sees as their business plan, I can promise you that. And even in the other aspect of this, the Dr. Austin referred to in terms of the fact that we do have the capabilities at the NCGC for doing this kind of high throughput screening to look for compounds that might ultimately be valuable in the long-term.

It's many, many steps, and the main focus would be on rare diseases that Novartis and other pharmaceutical companies are really not interested in. So, I think you have misunderstood, there is the circumstance here, we are fully aware and find very valuable, our opportunity to work with the private sector in this area, and in many others, and what you are hearing about here is building a niche which the private sector really would not be interested in putting their resources into.

Dr. Robert Kavlock: This is Bob Kavlock at EPA, I would just like to add that I think one of the unique things about our partnership, that we are developing, is that will been done in the public domain. All of our information will be released publicly, so that scientist can look at it, the public can look at

it, and the regulators can look at it. And I think that's a major difference between what that happens in the private sector in the pharmaceutical industry and what we are trying to do here. And I think Ray Tice here also has a statement to make.

Dr. Raymond Tice: Well, actually you said it Bob. This is Ray Tice; the only other thing I would point out though is that they are not going to be testing the same kinds of compounds that we test. And so our focus is on things that pose environment hazards to human, they are looking at a specific class of drug that might be beneficial. And again they keep that data private. One of the biggest problems is trying to get the release of information that they have, so that we can use it as part of our process of moving forward.

Male Speaker: I think that's a real problem there, that's when you should really be addressing.

Male Speaker: Yes we --.

Male Speaker: And I think they have their tremendous libraries have many of the compounds you are interested in.

Male Speaker: We are running out of time, let's move on the next question please.

Operator: We, will go next to (Larry Greenmyre) from Scientific American, your line is open.

Larry Greenmyre: Hi, was hoping you would talk a little bit more about the technology behind this, there has been reports of meta chips and data chips that have been used -- are there any breakthroughs on the technology side

that are enabling this, or it just more an announcement of that this work is being done?

Larry Thompson: Dr. Austin would like to answer that sir

Dr. Christopher Austin: Yeah. I think Bob Kavlock mentioned -- mentioned just a minute ago. There are many ways to approach this problem and many different types of assays, of the -- and we are going to use all of those, yes the meta chip that you are referring to is something that we are actually quite familiar with and are interested in using in this collaboration. So -- so, yeah we are always looking for new technologies, always looking for new ways to approach this problem. The problem with a lot of those technologies like the meta chip is that they are just not high throughput enough, that fundamentally what when it comes down to frequently.

Larry Greenmyre: Thanks.

Larry Thompson: Let's go to next question there.

Operator: We will go next to (Lisa Buffy) from Pesticide & and Toxic Chemical News, your line is open.

Lisa: Hi I have two questions if possible, first of all --.

Male Speaker: As long as they are short.

Lisa: That allows me -- but take what you can.

Male Speaker: Okay. Please proceed.

Lisa: First of all if there are limitations to animal testing and the existing data to which we will be comparing the new test results that you did and from animal models how do you address that uncertainties. And my second question is that I have there some toxicologist criticize some of these assays saying that toxicity is not a fact, it's just a cell or cells but a whole animal, so how do you plan, on addressing those concerns?

Dr. John Bucher: Well, this is John Bucher, I think what were part of this breakthrough if you will is the correct recognition that toxicity pathways as -- as identified by the national research council are really conserved to cross species and we know enough now about how sales responds, how organizations response toxic agents that we can try to design systems that we will allow us to probe those particular pathways, such that the data that we get will be applicable both to animals and to human. So that's how we hoped to bridge that particular problem.

Larry Thompson: Cool, can we go to the next questioner.

Operator: We will go next to Bob Grant from The Scientist.

Larry Thompson: Okay.

Bob Grant: Hi thank you, I'm glad I finally get to ask my question. Anyone free to answer this, but Dr. Collins said in the beginning that you guys didn’t get together this morning and decided to pursue this line of inquiry, and I know, there's nothing particular new about have you put testing or computational toxicology and there's certainly nothing new about in vitro assays. So I'm wondering given the fact that I'm carrying very

little about specifically, the infrastructure this new collaboration on what's the news here really?

Larry Thompson: Dr. Wilson would like to answer that?

Dr. Samuel Wilson: Yeah I think the news is the capacity to test many thousands of compounds over a broad concentration range and against the whole range of target cells or target cell chemical pathways. And that is a capacity that we really haven't had until this collaboration. I will stop there.

Larry Thompson: Okay.

Dr. Robert Kavlock: This is Bob Kavlock at EPA. I would say, what's new is that we are really laying out a very logical framework to use these technologies, to understand them, and to bring them into a situation where they can be used in a regulatory framework. This really takes a systematic approach of examining these and comparing them to traditional approaches and to -- and to gaps in the traditional approach. And I think that's what really new that there is a strong commitment by three organizations, you study this really in-depth and to make to progress on it in a very rapid fashion.

Male Speaker: Does anyone care -- I'm sorry, does anyone care to flush out that framework, I'm not hearing a lot about the specifics of how data is going to be shared between agencies or the funding that's behind us, anything like that?

Male Speaker: Sure.

Dr. Elias Zerhouni: I think -- this is Dr. Zerhouni, I think there is no question what you are seeing is the combination of the 30 year history of the NTP the National Toxicology Program, where there are 2500 very well documented compounds with very, very specific animal phenotypes which have been characterized over the years which we well know. Then you have the EPA, a knowledge based which is then combined with what we do best which is the issue of using our scale testing of hundred thousands of compounds and like 15 different concentrations you know, hundreds of different assays combined this into the same format as we have in pubcam.

If we go and visit pubcam, you will see that all of what we do for beneficial research in other words finding therapeutics is made public. The same thing is going to happen here, but at the end here is the -- here is the dream, the dream is that could you in a battery of test end up with very specific molecular signatures that will be predictive of human toxicology in ways that you just can't do in animal testing today. That is the value, in other words like I said it's one plus one equal three, the whole is much greater than some of the parts here.

Dr. Francis Collins: So, this is Francis Collins, just to answer your question then, what is the news, I think you have heard why this is the noble new paradigm for doing toxicology testing? What's special about today? Well there is this Memorandum Of Understanding signed by all three of the agencies which will be up on the web which you can look at, which lays out the agreement between the groups to work together, that's new. The paper and science magazine being published tomorrow, will in fact lay out this approach in a fashion that I promise you, both of the scientific community has not heard about, and if they look at the paper which I suspect many of them will, they will be excited about this.

I think this is not something that will be sort of, oh yeah we knew that, of course, if any new announcement of this sort you get together and figure out what the scientific opportunities are, so yeah we have been added for a couple of years getting to this point, but this is the launch. This is the moment where you can say we are officially starting something that could really change the way in which toxicology and compounds are assessed in the 21st century, we thought that was new.

Larry Thompson: So this is Larry Thompson, I'm afraid that we are -- we are at the end of our hour. I want to thank everybody for joining the briefing today. I want to remind you that the stuff is embargoed until 2 o'clock today with the science magazine and embargoed the paper. At that time and on all the websites of our respective organizations you will see lots of material going up with background information and the MOU and the scientific paper or the science paper. And I want to remind you that there is footage where you can go and look at the system, and you will get a little bit more of the sense of the physical infrastructure of it all which is very, very cool. And with that I would like to bring this briefing to a close, and thank you all very much for participating.

Operator: This does conclude today's teleconference. Have a great day. You may disconnect at any time.