ANSES

Chemical Mixtures

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ROUNDTABLE: HOW TO ADDRESS CHEMICAL MIXTURES IN RISK ASSESSMENT? WHAT ARE THE CHALLENGES?

Introduction

Stefan SCHEUER, Environmental and Energy Policies EU Affairs Consultant

I am a consultant working in Brussels where I have spent the last 13 years advising clients on European policymaking. I am not an expert in risk assessment, so I will be putting some simple questions to our panellists, although those can sometimes be the most difficult to answer.

Our roundtable is the final part of this two-day conference and I would like to broaden the perspective on risk assessment and move into the wider context of what the European Union is facing in terms of economic, social and environmental challenges and how risk assessment and risk management sit within that. The European Union has set itself the objective of dealing effectively with chemical mixtures by 2020. Seven years is not a long time, so there is much that therefore has to be done. The European Union is also dealing with other very immediate and urgent concerns, such as youth unemployment and economic and financial difficulties, and is facing a situation where the responses of the past to the economic crisis are not really working today. We therefore need to be aware that politicians and policymakers have at the forefront of their minds very different issues from those that we are dealing with here. Nevertheless, risk assessment, particularly for chemical mixtures, is a very important subject.

We have an outstanding group of people gathered together for our roundtable, comprising people occupying leading positions in the European Union and national risk assessment bodies, leading experts in research and representatives of civil society and the world of work. Each participant will give an opening statement and we will then look at particular issues and end the session with questions and comments.

Opening Statements

Timothy BOWMER, PhD, European Chemicals Agency (ECHA), Finland

The first thing that I would like to look at is the role that REACH has alongside other EU legislation. There is a large piece of relatively new legislation where some of the processes are just starting this year and will be fully on stream from 2014. With this new legislation there are interfaces with existing legislation, and this is an area of concern for ECHA because we are continually confronted with the limits of REACH and it will be very important to find a consistent way of dealing with uncertainty here. For example, in ECHA we decide on DNELs for chemicals that will apply in risk assessment while our sister committee in Luxembourg, run by DG Employment, decides on occupational exposure levels. The guidance for both areas is quite different and the way the uncertainty factors are applied here leaves us with discrepancies.

The second area that I would like to highlight concerns environment and has emerged only recently. In deciding on a restriction to a chemical on environmental grounds, we will be confronted, amongst other things, with Water Framework Directive monitoring data, which have their own reference values. If we therefore make determinations, there will be the issue of whether these will be in line with the directive's reference values. Another question will be whether we can use their monitoring data in our risk assessments in a coherent way.

Stefan SCHEUER

That touches on crucial aspects of regulatory interactions and uncertainties, and we will return to this subject later.

Tony MUSU, PhD, European Trade Union Institute (ETUI), Belgium

I would like to give the view of the workers, as I am a trade unionist and work for a research institute attached to the European Trade Union Confederation. The problem of chemical mixtures is extremely important to workers and when we look at all the occupational diseases that are recognised in the EU each year we see that one in three is caused by chemicals. There are 74,000 deaths of workers every year in the EU caused by exposure to hazardous chemicals and the reality is that this is exposure to different substances at the same time rather than to a single substance. A survey undertaken in France has shown that most workers are exposed to up to five carcinogens at the same time, so this problem clearly needs to be tackled urgently as it is causing a lot of disease and death.

Stefan SCHEUER

Thank you for informing us of these shocking numbers and of the urgency of the matter.

Bernadette OSSENDROP, PhD, National Institute for Public Health and Environment, (RIVM) Netherlands

My background is partly a national one but I have been mainly involved in EFSA in the area of cumulative risk assessment. We heard yesterday from Hermine REICH that the PPR Panel has issued four opinions, with the first exploring methodologies for assessing cumulative risk in pesticides and more recently we have had the cumulative assessment groups and the opinion on similar mode of action. These are all worthwhile activities and they are quite new, in a sense, but EFSA's Scientific Committee is also trying to harmonise issues within the different areas of legislation. Where ECHA deals with REACH and pesticides, we deal with legislation that covers pesticides, food contact materials and additives, as well as contaminants, which cannot be regulated as they already exist. While the Scientific Committee therefore works on the harmonisation of the different areas that EFSA is involved in, it is also important to go beyond that into other legislative frameworks and I certainly recognise that there is a range of uncertainties that we need address.

We have realised that what we are doing in respect of pesticides is not feasible for contaminants and with the hazard-based approach to everything that can be encountered from an environmental source it is not really possible to work on all these natural chemicals at the same time. There is therefore no one size fits all answer to this and it will be necessary to look at the different frameworks when addressing mixtures. Pesticides have been selected on the basis of their biological activity and are therefore a special group, whereas the situation is possibly different for contaminants.

Another area that needs to be explored further and which is the number one priority of the Scientific Committee is the biological relevance of toxicological effects. Not all effects are adverse and the human body is clearly capable of adapting to stimuli from the outside world. We therefore need to focus on how we are dealing with the adverse effects of adaptive responses.

Stefan SCHEUER

It is very intriguing to think about how we are adapting to chemicals.

Cynthia RIDER, PhD, National Institute of Environmental Health Sciences (NIEHS), United States

I am delighted to be here representing a testing agency and I would like to focus on receiving input from risk assessors in terms of areas for testing. In the mixtures workshop, we heard a lot from risk assessors who said that they preferred whole-mixtures approaches and we had the example from Richard HERTZBERG where the Office of Water at the EPA wanted to look at whole mixtures and bio-assays and testing the potency of mixtures. However, in practice we see a lot more of component-based risk assessment. We would therefore like to receive input on what direction we should take in the future and how we can maximise the impact of our testing and find ways of working better with Europe.

Stefan SCHEUER

Thank you for that perspective of cooperation.

Professor Gilbert SCHÖNFELDER, Bundesinstitut für Risikobewertung (BfR), Germany

The lesson that we have learned from yesterday's meeting is that we know nothing. However, we actually know that we know nothing, which is important, and the question is how we can solve the problem coming from different parts of the world and raise different issues. We have heard about occupational and cross-contamination by environment issues and what the differences are when compared with pharmaceuticals. We have therefore had a range over the past two days that has covered everything and the question now is how we can solve the problem.

I think that we need to simplify the system further because even for environmental contaminants at times we still do not know what effects and adverse effects are or what the right risk assessment should be. We are now making the world more complicated because the public has highlighted that we need to deal with mixtures and the question is how the technologies can offer something different when we try to solve the problem. If we want to compare the test strategy and bring it up to the level where we can see how human health, the environment and the ecosystem are affected, we need to understand which technology needs to be used. Most of the risk assessments have been done on animals, with many experiments carried out in in vitro studies, but we need to solve the problem of chemical mixtures very quickly and if we use animal testing it will take another 10 or 20 years before we get a better idea of this. We therefore need to have technologies that will give us more evidence within a shorter timeframe. It is important that we understand how we can benefit from in vitro systems and translate the data into risk assessment for humans and the ecosystem.

Stefan SCHEUER

Thank you. You made a philosophical observation at the beginning and to paraphrase SOCRATES, wisdom is to know that we do not know. We are therefore probably becoming wiser over these two days.

Lisette VAN VLIET, PhD, Health and Environment Alliance (HEAL), Belgium

I am delighted to be here today as a representative of a public interest, non-profit group. The Health and Environment Alliance is made up of environmental groups, health groups and professional public health research institutes and so on across Europe and our interest is in making sure that our environment is not making us ill. We see rising rates of chronic diseases and there are signs to indicate associations with single chemicals and mixtures.

There is therefore an urgent need to stop ignoring mixture effects, yet we can only see a few patchy requirements in terms of European Union policy. We see a little bit in terms of pesticides and cosmetics, but in the sectors responsible for chemical exposure there is no overarching legal requirement on mixtures. It is therefore imperative that EU laws change and a report from 2009 has already recommended that the legal mandate to deal with mixtures risk assessment should be strengthened.

We have heard today and yesterday that a lot of exposures, response curves and benchmark doses are mainly unknown and are likely to remain unknown for a long time, which we believe leads us to two options that are not completely mutually exclusive. The first is to explore the use of mixtures assessment factors or uncertainty factors in doing the risk assessment after having established a legal requirement and the other is not to wait until we have all the science, which could take the passing of a generation or two, but to eliminate certain exposures as quickly as possible. This is a real challenge, but I do not believe that it is out of proportion with the diseases that these chemicals could be causing in people.

The European Commission expects to produce technical guidelines on mixtures assessment in June 2014, and this will in fact emerge before its report scheduled for June 2015 on developing approaches on mixtures assessment. This appears to be putting the cart before the horse. We urgently need a legal requirement that crosses the different sectors.

Stefan SCHEUER

Thank you for your clear point on speeding up action on risk management.

Professor Marco VIGHI, DG Sanco Scientific Committees' Recommendation on Cumulative Assessment, Milano University, Italy

My position is slightly different from that of my colleagues as I am eco-toxicologist and my expertise is on ecosystems and not human health responses. Although I was a member of the Scientific Committees at DG Sanco for more than 20 years, I stopped being a member three months ago, so I am basically here representing myself as a scientist rather than as a representative of DG Sanco.

In terms of the problem of mixtures and ecosystems, the general principles are the same as with human health, and this was clearly highlighted yesterday by Sibylle ERMLER. There are a lot of common points, but there are also important differences. In terms of the differences, firstly, in ecotoxicology, protection is not about individuals but the structure and function of ecosystems, and this has led to major differences between human toxicology and ecotoxicology. Secondly, the mode of action in dealing with mixtures is fundamental because in complex communities all organisms are different and respond differently to chemicals. Thirdly, exposure is quite different for ecosystems compared with human health. All these differences must therefore be taken into account, including when dealing with the regulatory approach.

Stefan SCHEUER

Thank you for pointing out those further layers of complexity. We will now turn to the issues. The conference has set out to present the state of play on risk assessment and dealing with chemical mixtures, to identify trends and research needs and to show what may and may not be expected from risk assessment in the future. I will begin by asking Timothy to tell us whether the discussions have provided him with answers to the questions that he faces in a regulatory setting.

Issues

Timothy BOWMER

That is a very wide-ranging question. The conference has been useful in recapping matters from a transatlantic perspective and showing that things have not been static. Several significant reports have been produced in Europe recently, which should help matters and the encouraging message is that things have not been standing still.

Stefan SCHEUER

Marco has also played a role in risk assessment and Scientific Committees. Have you been given new answers and priorities through the conference?

Marco VIGHI

I think that the conference has more or less confirmed what the Scientific Committees in DG Sanco had basically established in that the current state of the art in respect of mixtures is sufficiently advanced for regulatory proposals to be made. Nevertheless, that does not mean that there will be lots of improvements because science is a never-ending story. I think that the conference has confirmed that the synergy point is the weakest area and one that probably needs more attention.

Stefan SCHEUER

Could you give us any examples of the regulatory approaches that are needed?

Marco VIGHI

In way, a regulatory proposal was put forward in DG Sanco's Scientific Committees in 2011. In general, the approach can be taken as a conservative starting point. It depends on the kind of regulation we want. On the one hand, we have approaches, such as REACH, with their focus on chemicals and the pesticides, while on the other hand we have more environmentally focused approaches such as the Water Framework Directive. I believe that both these completely different approaches have to be considered. With REACH and the Pesticides Directive, we can consider technical products relating to mixtures with different active ingredients and other kinds of additives. With the environmental approaches, we have mixtures that originate from different human activities within a given region and the composition of mixtures that can be present in the environment is much more complex.

Stefan SCHEUER

Moving to our representatives from civil society, what have been your take-home messages, particularly in light of possible imminent decisions on regulatory approaches?

Lisette VAN VLIET

The idea of viable regulatory approaches has been around since 2009 and we have had confirmation of that here. A lot of what I have heard relates more to the further development of the science and less to an overall for policy advancement, and this has come through indirectly in some of the presentations. However, most of the conference has focused on pesticides, yet as regards food contact materials I understand that there are possibly 100,000 reaction products and in the current legislation on food contact materials only 3,000 of those are being controlled in terms of carcinogens, mutagens and reproductive toxins. We have not even addressed endocrine disruption issues. There are therefore enormous gaps and we desperately need to see major policy advancement and it is frustrating that a lot of time is being spent on estimations on pesticides while these other matters are not being discussed. We urgently need a European call for mixtures assessment in as many different sectors as possible to make sure that we bring ourselves up to date with what was set out in 2009, which recognised that we have methods for doing risk assessment for mixtures and that we need to get on with it.

Stefan SCHEUER

You are therefore saying that there is too much focus on research and not enough on action.

Lisette VAN VLIET

I am saying that there is a lot of research on how risk assessment can be improved. However, risk assessment that is not being applied to risk management across sectors that have not even come to grips with mixture assessment will not help to solve the ultimate problem.

Stefan SCHEUER

Gilbert talked about simplification.

Gilbert SCHÖNFELDER

This may be my own story. I am still an academic with the university but before I worked for BfR I was solely an academic and I focused on whatever I liked. I was particularly interested in endocrine disruptors and had been working on the area since 2002. We are now in 2014 and we still do not know everything there is to know about endocrine disruptors. In fact, our attention over the past 10 years has been misplaced in some cases because when looking for adverse effects in the classical endocrine system the focus was on the steroid hormones and we concentrated on endotoxicology and so on. Then a couple of papers were written by epidemiologists that showed that there was no really good data demonstrating a deep influence of endocrine disruptors on the reproductive systems when compared with humans and it was suddenly demonstrated that it related to cardiovascular and metabolic diseases. As a result, for people who had been focusing for years on the typical developmental, reproductive and fertility fields, the whole area was opened up. The question is therefore how

can we solve the problem of chemical mixtures if we still cannot solve it for a single compound?

If we take the discussion on BPA and the estrogenic effect, we heard about the strategies for testing where you take the water, fraction it, put it on an assay and see whether that gives you a clear answer. People were looking for estrogenic activity by testing whether the ER was activating in a special gene, for instance. However, I can point to research data where the single assay is not good enough for screening for an endocrine disruptor focusing on estrogenic activity because it all depends on the difference in a single base within a chromosome that could mean that the ER is no longer functional. How can we therefore solve a complex system if we do not yet have the ability to solve the problem with a single compound?

I therefore think that simplification is the most important issue and the outcome of our meeting is that not only do we not know what we know but that we have to focus as agencies. We are the BfR, the DTU and Anses and the good thing is that these three key players in Europe are focusing on issues other than occupational exposure, which is in fact not part of our focus. However, we need to find strategies, without everybody focusing on the same thing, and decide on the first step and then go further up the ladder.

We now have an overview of what might be addressed and what the first step is that we need to take. People are moving from pesticides because compared with environmental contaminants there are only a few pesticides while there is a broad range of datasets historically. For people dealing with chemical mixtures, it is easier to deal with historic data and compounds as they are better known. At BfR, we started with triazoles because we knew that we had good data for looking at the problem of reproductive effects such as fertility.

Stefan SCHEUER

You are therefore saying that what has come out of the conference for you is that you have a clearer picture of what can be done through better cooperation between agencies and that there are probably other people who could be brought in. However, you are pointing to an enormous complexity and as we look at increasing uncertainty, what would that mean in terms of meeting Europe's 2020 objective to address chemical mixtures and minimise the risk in establishing a comprehensive database in this area? Is this achievable or do we need to involve other people? If so, what other agencies or regulatory bodies do you think should be brought in?

Gilbert SCHÖNFELDER

I think that a lot of people are already involved. You keep meeting the main agencies at the different events, including agencies from the United States. We heard that the US has its own strategy through the National Toxicology Program and I liked this programme a lot when I heard about it today because it says that this is not about just a single test but needs to be a summary of all the different tests. We therefore need to judge the compound by summarising everything rather than through any single answer. That is a more helpful strategy, especially given the timeframe that we have to work within. You were talking about uncertainties in terms of policy and whereas the policy now requires us to solve the problem within a couple of years, if you use the data from animals, for instance, it will take us 20 or 30 years. The issue is therefore about doing it as quickly as possible.

It is good to bring people together and discuss how we could collaborate. The first step for the three of us is to identify what it is that we want to tackle and then take it one step at a time. Occupational exposure has a particular timeframe where people are exposed during

their working lives - probably for eight hours each working day - and the exposure rate is much higher. With a single compound or two or four compounds, you will be exposed to a much higher level than someone active in the general environment, where there is cross-contamination of everything and low-dose effects. Occupationally, there are therefore generally higher exposure levels.

When we talk about environmental exposure, we have to keep in mind occupational exposure, but this is very close to what we know with pharmaceuticals. When you get older you are treated with more drugs and most people between the ages of 60 and 70 are taking six to 10 drugs per day, with a combination of different drugs with different modes of action. With occupational exposure, it is generally the same. In your working life, you are generally exposed to a couple of compounds – it is certainly not hundreds or thousands – depending on where you work.

Tony MUSU

I would like to return to what Lisette was saying. At some point in time, we will need to have a clear legal framework to address the problem, so I agree with her fully on that point. However, the real question is what do we do in the meantime? Today, workers are exposed to many different chemicals. We can take the example of a French project called GISCOP on occupational cancers, where they are trying to understand the exposure patients with cancer had when they were at work. This shows that there are number of cocktails that are often found at the workplace, such as in the paint industry, where chromium, nickel, lead, cobalt, and cadmium can all be present.

We therefore need actions for solving today's problems and must implement the current legislative framework more effectively. REACH has been a positive move because it will make progress on the data that is lacking on all the chemicals that we are exposed to, and there is also the legislation on the protection of workers where employers are supposed to carry out a risk assessment of the workplace and generally take into account the combined effect of the different chemicals that are present. Therefore, before waiting for progress to be made on risk assessment on chemical mixtures we need to ensure that the current legislation works better and to have synergies between REACH and the legislation on the protection of workers. The link between the DNELs that are derived under REACH and the ~~OALs~~ OELs under the legislation on the protection of workers is a key issue that needs to be discussed and I would agree with Stefan that we must explore these relationships between the different pieces of legislation that already exist today and work together more effectively.

Timothy BOWMER

I would like to reflect on what the last few speakers have said. We need to use the tools that we currently have effectively. We know that the research will take time and there will also probably need to be changes to the legislation. Nevertheless, we currently have some good tools for dealing with dangerous chemicals and one that is often forgotten about is classification and labelling, mainly because it is hazard based and probably not very attractive to scientists as there is no risk involved. However, this is a kind of blunt heavy instrument that can be used to bring chemicals into line for other areas of downstream treatment and regulation. For example, CLH is aimed at both single substances, and mixtures and preparations and it also has provisions for downstream use in other mixtures, which is sometimes forgotten. Every chemical that is classified has a generic concentration limit above which it cannot be used in a mixture. If we then believe that there are high-potency substances for which those generic concentration limits are not sufficient, we can apply specific concentration limits and depending on the science and the toxicology in

particular we can take these specific concentration limits down to quite low levels. We need to focus more on these relatively simple measures.

To give a research example where some help is needed, if a substance has a clear animal database, we simply use that and have a threshold for determining the high-potency substances and can then give them an appropriate specific concentration limit. Ironically, if the database relates to basically human experience rather than animal studies, there is no guidance and in committee we have to look at things on a case-by-case basis. There is therefore a need for someone to consolidate these databases and bring this into guidance so that we have a more supple approach.

As regards CLH, we have been moving this process forward at ECHA. We are currently working on about 40 substances per year, depending on how many are submitted by the member states, and I think there is also a case for collaboration between member states here. Not all member states make submissions, but there is in fact no need for them to do so alone and smaller member states could collaborate and ensure the process keeps moving at high speed.

Stefan SCHEUER

Clearly, a response to growing complexity can be through using simple answers and something which is often possibly seen as being too blunt and not meeting the strictness of scientific research. However, perhaps this is the kind of polarity that politicians have to deal with. Turning to Cynthia, what is your experience in the US in terms of complexity and simplicity in risk assessment?

Cynthia RIDER

I can give you a couple of good examples of agency collaboration on regulation. Firstly, the EPA asked the National Academy of Sciences to review whether or not cumulative risk assessment should be carried out on the phthalates. The decision was then taken to include other anti-androgenic chemicals and things were not put into silos according to personal care products or phthalates plasticisers or pesticides but went across areas. The agency paid close attention to the input and we had the example of cardiovascular disease that Rick spoke about earlier where they looked at developing a framework for cumulative risk assessment and moving backward from a disease to try to identify all the stressors that could affect the disease and use available tools to complete a risk assessment regardless of whether or not they had jurisdiction over controlling access to medical care. This is a clear example of where the science has fed into driving actual risk assessment processes and recommendations, which I think is very promising.

Marco VIGHI

We have the regulatory tools and we should use them. With environmental protection, under the Water Framework Directive, water quality standards are developed for individual substances. However, the quality of the ecosystem needs to be evaluated on the basis of biological quality, which is the result of multiple stress factors and therefore implicitly considers the concept of mixtures, and that is already in the current regulation.

Stefan SCHEUER

That is an important point. However, the latest river basin management plans looking at the Water Framework Directive in terms of whether the ecosystem objectives have been

achieved showed that for large parts of Europe there was still a lot to do. It remains difficult to take action because you do not know exactly how and where to act and which stressors to deal with first, and prioritisation continues to be a problem. Europe's water systems continue to be in a poor state. This therefore does not really help us here.

Marco VIGHI

That is right. However, this is the consequence of the lack of data and not a fault of the regulation. We require an enormous amount of information regarding the proper application of the Water Framework Directive and it is still not there in many member states. Nevertheless, I believe that the regulatory tool is the right one.

Stefan SCHEUER

How do we adapt to the stressors? We have an opportunity to adapt to environmental stress and chemical risk.

Bernadette OSSENDROP

I did not mean earlier that we would eventually have to evolve or anything like that, but was simply referring to the homeostasis that every human being has. There is a certain level to which people can respond to external stressors and it is what that level is that we are discussing, and when you go beyond it there may be adverse effects. That is what struck me with all the results from the cell systems and you cannot always be sure what this will mean for a live human being or animal, which was also the question being put by those who presented the results. This is a big challenge for us.

Since I began working with EFSA in 2006, there has been a real increase in collaborative projects with ECHA, DG Sanco's Scientific Committees and other agencies and that is the starting point for having a more harmonised approach and learning from each other. Initiatives such as those with Anses, DTU and BfR are very important for complementing this and this conference has brought together scientists with very different backgrounds. I have noted that in a number of cases presenters did not immediately understand the questions that had been put to them because of these different backgrounds and I believe that we need to get a better understanding of each other's terminology and bring the work forward by talking about exactly the same thing, which is also something that I think Bette MEEK was referring in her presentation. We need to be precise about what we want to achieve.

We already have a lot of good tools and are making progress. You could get the impression that we are just at the beginning and that nothing is being done, but I do not think that that is the case. Even by doing single chemical assessments we are already doing a good job of protecting the public, but we can do better.

Stefan SCHEUER

Do you think that the European Union's objectives for 2020 are achievable?

Bernadette OSSENDROP

That is a very difficult question. I think that we can go a long way towards achieving them but there will definitely be issues that will remain in 2020.

Stefan SCHEUER

Do we need to increase capacity and cooperation? What is the magnitude of the challenge? In the end, it probably comes down to available resources, so do you have the staff, capacities, budgets, testing labs and so on that you need?

Bernadette OSSENDROP

Clearly, things will happen more quickly if we have more resources. Nevertheless, having more resources will not make everything happen more quickly because your thinking has to evolve and you have to reconsider what you have been doing in pilot experiments, for instance. It is therefore not always about money. The question of extra resources then takes you into the realm of the risk managers and politicians who have to decide whether it is more important to tackle unemployment or the assessment of mixture toxicity. That decision is not part of EFSA's remit.

Gilbert SCHÖNFELDER

I believe that a key word here is 'translational', which is a very popular word that is being used more and more in the scientific literature, with translational medicine and translational toxicology, for example. Bernadette was talking about who was attending the conference and we have toxicologists, chemists and biochemists, but what about the medical doctors? We heard about the occupational effects and going into hospitals to ask people affected by cancer what they worked at and what their exposure was. I am a medical doctor who trains students and we teach environmental medicine. The students tell me that they do not care about environmental medicine because they feel that they cannot manage the problem of risk assessment and toxicology. The feeling is that people know that they are being exposed to chemicals but they do not care whether they have a disease or not because they cannot do anything about it. I tell my students that in terms of prevention and public health we need to have their data on the symptoms. When patients go to the hospital we diagnose symptoms but we do not ask them how it has come about that they have the disease. Getting the translational data to interpret adverse effects from in vitro testing and being able to identify whether the disease is severe or not is very important and this is not happening. We are always acting separately. There are meetings where toxicologists are involved, but we need to include the clinicians.

Everybody is talking about cardiovascular disease, but this is because of the JAMA paper on BPA, which was the first paper to show that an endocrine disruptor does not lead to cancer or infertility, but that they had a metabolic syndrome. Suddenly, everybody is addressing a topic that has not been the focus of even an OECD guideline for 20 years. In terms of guidelines, no-one is really looking at whether a chemical can lead to high blood pressure, despite high blood pressure leading to most deaths in the world. High blood pressure has not been addressed apart from our understanding 20 years later that chronic exposure to lead leads to high blood pressure, through findings in kidney disease.

The problem is therefore translation in terms of the meaning of the result in the clinics and then going back from the clinic to the in vitro experiments. However, most clinicians are not dealing with toxic effects and there is no sense of scientific focus on the main question.

As regards the ecosystem, eco-biodiversity is very important because if we are dealing with very severe effects then it comes back to the old concept of evolutionary medicine. We then have the question of what will happen in 10 years and then in 100 years in terms of trans-generational effects. We need to work with evolutionary models, and biodiversity and

ecosystems help in this regard because with species we can have five generations in less than a year and can therefore extrapolate from that what might happen with humans. Evolutionary toxicology is therefore a step forward and could be a new technology that we could address, particularly for chemical mixtures. Even if we do not know what different chemicals we are being exposed to at the same time and what the amounts are, evolutionary systems can help us deliver some of the most effective answers.

Stefan SCHEUER

I would like to go back to the important motivational problem that you mentioned about doctors trying to deal with things that they feel they cannot do anything about. How were you able to motivate them?

Gilbert SCHÖNFELDER

I simply asked them to think about what they were wearing and then consider how different colours were added to cotton. I also asked them to think about the plastic bottles that they were drinking out of and whether anything could be emanating from the plastic into the water. Some then saw that there was an issue while others did not see it as important. However, I got a discussion going, which is the key thing.

Stefan SCHEUER

It is a very important topic and it brings us to the question of decision-making procedures and what individuals can do in terms of taking action themselves or ensuring that their representatives are taking action. What governance tools are available for dealing with the risks from chemical mixture? We have the precautionary principle enshrined in the European Union treaty, which has led to lengthy discussion with the US on what that should mean. There is also substitution and the no data, no market principle under REACH and in terms of public participation we have the involvement of non-experts and the recognition that risk perceptions are changing over time.

Timothy BOWMER

I would go back to the point on making existing legislation work as seamlessly as possible and ensuring that there are effective interconnections between REACH and the other pieces of legislation. For me, that is the most important way forward.

Stefan SCHEUER

Do you think that any specific tool needs to be strengthened?

Timothy BOWMER

I work exclusively on REACH and classification labelling. The final pieces of the puzzle of REACH are only being put into place this year and there is still much that needs to be done. I believe that REACH will work, including for mixtures, although I cannot say if it will be by 2020.

Lisette VAN VLIET

I would be curious to find out how many people in the audience think that a mixtures assessment factor is a good way of proceeding. We can see that fewer than 10 people think that it is a good idea. How many people think that this is something that we should not do? We can see that about the same number of people think that we should not do it.

Stefan SCHEUER

There is a lot of uncertainty.

Lisette VAN VLIET

I think that that tells us something.

Marco VIGHI

With mixtures, we are talking about three different levels of problems. Firstly, we have commercial products, which can be regulated through chemical regulations. Secondly, we have mixtures produced by specific human activities, such as industrial discharge or crops where a number of chemicals are discharged – and this should be controlled by emissions-based regulation. Thirdly, we have mixtures that can occur in the natural environment and which is the result of different activities, with different kinds of discharges. This can only be regulated by approaches such as land use intervention. Regulation such as the Water Framework Directive can help here. These are therefore the three levels of instruments that are available and they have to be applied in the different situations for different kinds of mixtures.

Cynthia RIDER

From a US perspective, the Food Quality Protection Act and the Clean Water Act are two relevant pieces of legislation. However, at the NIEHS and in NTP in particular we are strictly bound not to cross over into the area of risk assessment as we supply unbiased data for other agencies to carry out risk assessment. Our job is to provide the context and show the relative toxicity of different materials so that those carrying out risk assessment can make their decisions.

Bernadette OSSENDROP

Risk management is not part of EFSA's remit, but I agree with the previous speakers in terms of ensuring that the current legislation works - and it is also needs to be harmonised - and while that is not necessarily the management option, it is a major priority. One option that you can provide risk managers with is taking a compound off the market, although other compounds can then replace what has been removed and even less could then be known about these others. Decisions therefore need to be made on a case-by-case basis.

Tony MUSU

My preferred option is substitution. One of the main aims of REACH is to phase the main hazardous chemicals out from the market and companies have to obtain authorisation if they

want to continue to use a hazardous substance. At the moment, the authorisation system under REACH works very slowly, with about 1,500 substances of high concern in the EU but only 144 substances on the candidate list for authorisation. The system is good in principle because the idea is to push for innovation and replace the most hazardous substances with safer ones. However, things move too slowly and we need to work on speeding the whole thing up. The member states and the European Commission recently adopted the SVHC roadmap where the idea is to include all the relevant substances of very high concern in the candidate list by 2020 and my hope is that this will help speed up the process.

Gilbert SCHÖNFELDER

We have all the subjects that have already been mentioned, but what has not been highlighted is risk communication, which means giving responsibility back to consumers. It is important for agencies such as ours to work effectively on risk communication beyond what is being done in the press and provide an objective view on the compounds and let consumers then judge for themselves. It is very simple – we must give them the tools. We have to teach simple statistics at school so that people can understand what having a 50% or a 90% chance of acquiring something means. We therefore need to give people tools at school or more generally for the public through risk communication so that they can develop their own viewpoints from the beginning. Before we solve the problems that risk management attempts to deal with, we can start with risk communication. Objective risk communication gives responsibility back to consumers and allows them to judge for themselves. However, there has to be a fair database and the information that we, as scientists, members of agencies and regulators, provide must be as objective as possible.

Stefan SCHEUER

Thank you. I think that we have explored a large area and showed that it is difficult to go beyond the world of risk assessment as a method and building block in a larger setting as there are different pieces of legislation that have their own focus and different sciences. We also moved into the area of public communication.

We will now open up the discussion to the audience.

Discussion

Tony FLETCHER, London School of Hygiene and Public Health, England

Sometimes research on mixtures shows a dramatic combined effect and at other times it shows nothing. When we were asked whether we supported the idea of there being no more safety factors or a blanket safety factor I was one of the majority who abstained from expressing a preference. A case-by-case approach seems to be more appropriate, but there are millions of combinations that you could think about. The example given by Anne-Marie VINGAARD of testing in the presence of a cocktail of the chemicals that are plausibly part of the general environment and are there at levels that are relevant was interesting and it led me to think that that could be a blanket test that we could add to REACH. As well as testing individual chemicals, a cocktail of chemicals could therefore be agreed via some mechanism and applied universally. I then thought that that might not be such a good idea because even if the perfect cocktail existed now, it would probably take about 10 years to negotiate it and by the time it was set up and implemented it would be irrelevant. This might therefore be a good option for research rather than for regulation. We could re-test within a short timeframe the 50 most interesting chemicals that we are likely to be exposed to at levels that are

relevant and so get much more consistent data on a heterogeneous mix of chemicals and be better positioned to decide whether it would make sense to have a blanket control or not.

From the floor

We have learned that we have a very big challenge and this is a programme that is probably more complex than the human genome programme. However, that should not stop us from taking action and making decisions or acting on what we already know. Part of the science is already there. I do not agree that we do not know anything; we know a little about a lot of different things. Therefore, while we still need to know a lot more, we already know something and we could make use of what we know. For example, we talked a lot about the additions for mixtures, but the dioxins and toxic equivalence have been there for a long time. We could get some inspiration from that – and in fact that is actually what is happening.

In terms of taking advantage of what we know, we sometimes tend to oppose things, and here I would like to take the example of the difference between adaptive mechanisms and adverse effects. This is absolutely true. We live in a chemical universe and are adapting all the time. However, that does not mean that the adaptive phenomena are not toxic in the long run. There is a cost for adaptation in the long term. The way we adapt is usually by getting rid of compounds through metabolism, although metabolism itself is a source of toxicity. We know that. We therefore have to think not just in terms of whether it is adverse or not adverse but also in terms of whether it is short term or long term and in that respect I think that mixtures can be an additional problem as they can influence each other's metabolism.

We therefore know a little and it is a big challenge for us to know more. We could try to increase the speed of translation and make it available for management.

Dave PARKER, UK Food Standards Agency

I voted against the assessment factor as I support the efforts on improving community risk assessment. Dr OSSENDORP and EFSA have provided a way forward with dose addition for dissimilar substances and we may also need to think more about individual variability in multi-cellular organisms and the environment. When looking at dissimilar substances where there is a chance that elements of homeostasis in different parts of pathways or metabolism, we might be underestimating their ability to work at the same time rather than overcoming one barrier and adding up. If we have a dissimilar acting substance we might also be less able to assume that for someone who is 100-fold from an animal in terms of targets for one endpoint there may be some variation there.

Bernadette OSSENDROP

I agree that we need further research on dissimilar modes of action and synergism and the most recent publication by the EFSA PPR panel has indicated that we could do a lot more on independent action with existing data from pesticide dossiers. We need to know more about the determinants of synergism and the toxico-kinetics and toxico-dynamics of interactions. Nevertheless, we have made a start and we know what the next step should be, and when we have taken that step we can take another step and so on. I was happy that a number of speakers stated that doing risk assessment on mixtures was an iterative process. We start doing it but we then stumble and see that something is not quite right or we need to take other factors into account. We then start doing that and on it goes. We cannot predict how we will be doing things in 10 years' time; we need to develop this as we go along.

Lisette VAN VLIET

If we are working iteratively and cannot predict how things will be done in the future, it does not seem like a very wise strategy to start with one domain at a time where the legislation already exists. I am definitely in favour of implementing the current laws more effectively and that is why I believe that the phthalates restriction case from Denmark in REACH is such a tragedy as it was the first attempt to really take into account the problems with cumulative effect, and my organisation does not think that the arguments against it were sufficiently valid.

We need to do this in a number of different domains at the same time and if we only do it sequentially we will not be doing enough to protect the public. Whether we are doing a good job at the moment is worthy of discussion itself but I think that there is a great deal more that needs to be done given the range of products and chemicals that are producing mixture exposures in humans. It is very difficult to say how good the job being done really is.

Gilbert SCHÖNFELDER

I have had something in mind for a very long time and I do not know why it has never happened. Epidemiologists look backwards and take either blood or urine samples and try to determine whether the samples have any signs of compounds. It will depend where they are looking as there is no single button that you can push where everything comes out. I understand the problems that exist, but we also need to think about the next 100 or 200 years and we are losing as each year goes by. Personally, I believe that we need to come up with a design for collecting human samples from the time of pregnancy to older age and get them to doctors and then figure out whether there are any symptoms. We need to monitor this for the next 20 or 40 years, starting with worldwide cohort where you sample either once or twice a year. I recognise that this would be very expensive but it is all that we have. We extrapolate from animal or in vitro experiments but we have no clear information on what is going on in humans. We need studies to begin now and end in 100 years' time, where over the years there is clear data on possible links between environmental exposure and disease. While we have the German cohort study, this does not look for environmental exposures. Nevertheless, there they are starting to sample 100,000 people and it will cost at least EUR1 billion. Through this study they want to find out what common diseases are linked to.

We need a design for the whole world where we sample and look at data from current observations. We can then study compounds that come in and out of the market and it will be much easier to make links compared with what we are doing at the moment.

Tony MUSU

I would like to add another layer of complexity. We heard this morning about non-chemical factors and we know, for instance, that working at night increases the chances of developing cancer. In the cleaning industry, for example, people work at night and they are also exposed to a cocktail of chemicals. We need to take this type of thing into account as well in our research.

Ulla HASS, DTU

We must have data on humans, but this has to lead to some improvements, such as fewer diseases or improved safety. If we keep on exposing people for 20 years or more to mixtures of endocrine disruptors, where we know from animal studies that the margin of safety is too low, we will see poor semen quality in young men. The regulators would then take some action, but it would be another 20 years before we had healthy young men again.

I am very much in favour of knowing what goes on in humans but we need to recognise that while some of the diseases that we worry the most about may be severe, they are also relatively rare and you therefore need extremely large groups to pick them up. Denmark as a country is not big enough for this, for instance. I would just therefore say a word of caution against that.

When we were asked about the mixture assessment factor a lot of people did not answer one way or the other, and I can see that this is a very difficult question to answer. However, I was thinking about it in another way. There is an old practice when it comes to looking at one chemical where you state that part of the exposure can come from the water and part from food and so on and you allocate different percentages to each commodity. This does not allow for the water to use everything that you can tolerate, for instance – you may have 20% from water and 20% from food and so on. Until everything has been implemented in the regulation and we have a perfect system, this could be a way of handling mixture effects so that instead of having the hazard quotient and being pleased that it is just below one, you would leave room for the other chemicals. Additionally, you might do mixed or cumulative assessment for pesticides and then do it elsewhere for the REACH chemicals and be happy that for both it is only 0.99. However, were you to add them together it would come to almost two.

Gilbert SCHÖNFELDER

My point was not that there would be a human study that would go on for 40 years before we regulated. However, I have been sitting here for 10 years now and nothing much has changed for endocrine disruptors and we still have the same issues of fertility and hypospadias and so on. People are still asking about what happens in humans. If I had had the money to start these projects 10 years ago, that would have been helpful. What I am saying therefore is that we should not wait any longer and need to come up with a study to address these issues in humans. That does not mean that we should stop regulating. Both the number of cases sampled and the dropout rate have to be very high, but that is what is needed.

We have had the topic of whether animal testing is relevant to humans, which has been in the press over the past six months because of the PNAS publication. There they compared human data on inflammation with mice studies and concluded that it was not possible to compare the human data with the mice data. The discussion then began on whether it was possible to extrapolate animal testing for human disease. We then come to the same point of needing good human data to be able to have more specific answers and I would bet you that if we do no start now we will be in the same place in 10 years' time.

From the floor

The people doing the clinical studies and human studies in Denmark are not here today but Nils SKAKKEBAEK started the endocrine disruptor field more or less along with Richard SHARP from the UK. A lot of studies have therefore been done and they have shown, for instance, that Danish girls are now developing breasts a year earlier than was the case 10 years ago. We therefore have human evidence that something is going on, and that cannot be related to obesity or hormone levels. It is certainly environmental and it could very probably be related to chemicals. We also have the decline in semen in young Danish men and many different kinds of testicular cancer are rising dramatically. This is not just happening in Denmark but is also happening in Finland and a lot of other places. There have also been studies in the US undertaken by Shanna SWAN in small boys, and not just in rats as we do. There is therefore a lot of human data and we should be doing something about this.

Gilbert SCHÖNFELDER

You are therefore fighting against my idea, but that is not what I was saying. The point that I am making is that the data are not good enough, not that there are no data. I could debate the SKAKKEBAEK and SWAN data with you and how good those discussions are. However, I do not doubt those data; what I am saying is that we need to have better data and a better study design. Defending that is probably the worst thing that you could do.

Stefan SCHEUER

When you say 'good enough' what do you mean that it should be good enough for?

Gilbert SCHÖNFELDER

The data simply need to be good enough for what we need to do now. We have no other data so the data that is there are relevant for now. People are discussing these data and you need designs of this kind. Otherwise you keep going back to the old discussions.

Tony MUSU

Perhaps it should be good enough so that we can start acting on the data and applying the precautionary principle.

Lisette VAN VLIET

They should be good enough to act. Again, if we look at what happened to the Danish phthalates case, the Risk Assessment Committee said that even though the human bio-monitoring data was only three years old it was not good enough. We can discuss what an outrage it is that we do not have an equivalent of NHANES in Europe and the attempt by the European Commission to cobble together environmental and human bio-monitoring data through the Joint Research Centre is fraught with difficulty. However, there is a real tension in trying to elaborate long-term research projects and then asking scientists to attempt to do translational work. We need to have clearer statements on the long-term research projects and where there is enough confidence in the data that already exist actions restricting the use of chemicals need to be taken, and that is where things appear to become very static.

Anne-Marie VINGAARD, DTU, Denmark

I do not think that we should be paralysed by the complexity of the problem. From a pragmatic point of view, we could use the hazard index for predicting mixture effects and the real limitation there would be on the data on single compounds. We would need a toxic measure and exposure data for each chemical. As Lisette pointed out, the real limitation is lack of data of single chemicals and there are thousands of chemicals for which we have no animal data and where will still have no data in the near future. We should therefore be open to applying in vitro data as a toxic measure and I am therefore very keen on the ToxCast programme that is creating a lot of in vitro data where for instance you could use an IC50 from an in vitro test as an exposure parameter for humans.

One limitation is therefore data on single compounds and another is that the information on toxicity and exposure is spread across different websites and reports where if you need to

predict the mixture effect of 10 or 20 chemicals, you have to spend a long time searching. It would therefore be help to have all the information brought together in some way.

From the floor

Perhaps we should take a two-pronged approach. The previous suggestion of using the hazard index when we have the information is a very good one because we have access to a lot of information based on single chemicals and we would at least be addressing a concern on dose addition, if one exists, without the need for a lot of new knowledge. For the other mixture problems, such as interactions, I was fortunate to have some funding to do a small study on low-dose synergy and despite some very poor communication of the results saying that we only found synergistic interaction magnitudes of threefold or less and that it was really not a concern at low doses, I have to say that the number of studies that we found that quantified interaction magnitude was extremely small and was limited to very small groups of chemicals. We had no endocrine disruptors, some pesticides and no metals. There are therefore certain groups of chemicals that could be investigated more thoroughly to see if there are low-dose interactions that are worth worrying about, considering the other uncertainties in human variability and exposure and so on, and we also need to worry about other diseases.

We then need to look at high-dose exposures, where we know that interactions can be extremely important. Smoking, asbestos, radon, carbon tetrachloride and ethanol are all high-dose interactions that are either lethal or cause cancer. We then need to see where we are likely to find those exposures to high-dose mixtures and avoid them. We do not need to quantify exactly what the consequences will be because there will be high doses and those will then be the interactions that will be really important from a health point of view. We can worry about avoiding those exposures without having to know everything about the toxic interactions involved.

Stefan SCHEUER

I would now like to summarise what has been said. There are a lot of different agendas and it is difficult to come up with a clear message, which ought to be of concern to everyone. I started by saying that this was an opportunity to broaden the perspective and talk about the big economic and political challenges that Europe is facing, as well as the scarce resources that need to be prioritised. I am afraid that it is becoming increasingly difficult to raise funds and get the attention from the political side to deal with the massive challenge of chemical risks, and that challenge has been there for all of the 13 years that I have been working on EU policy. We were talking about moving from analysis and paralysis to action 13 years ago and saying that taking small steps in the right direction does not mean that you will ever get to your objective. This therefore clearly reminds me of the past and the question of whether it is sufficient to move more quickly to have better outcomes.

Perhaps we could therefore have some final thoughts on what still needs to be done in bringing together different agendas, cooperation and the translation from the scientific research area to the regulatory and political arena and whether that should be one of the top priorities.

Gilbert SCHÖNFELDER

We sit together as three of the major agencies and try to see where we can collaborate and as a representative of German risk assessment I can assure you that we are already addressing this matter in our agency, otherwise we would not have agreed to highlight the

subject in the annual meeting held by all three agencies. As an agency involved in both research and risk assessment, this is a very important issue for us and we will face the challenge over the coming years.

Tony MUSU

We need to work on different fronts and advance research on risk assessment. However, we must remember that we already have a legislative framework that we need to use and we also always need to think about prevention and try to avoid using hazardous chemicals. I think that that would be the best thing that we could do.

Bernadette OSSENDROP

Your question reminds me of a presentation given by Professor Anne GLOVER, President Barroso's Scientific Advisor, last November, when she said that scientists had to stand together to give a single strong signal. We therefore need someone or something to pull everything forward. What we are all doing individually is very useful but it is only when we join forces that we can ensure that our message is heard in the right places.

Cynthia RIDER

This conference has been very encouraging and the message that has emerged is that people should do the best they can at this time and work to prioritise research in the future.

Marco VIGHI

I agree fully with the second intervention from the floor. There are many things that we do not know, but we do know some things and what we know could be enough for us to start to do something. The case-by-case approach is obviously not acceptable, but there are certain possibilities for models that could be applied and there is enough consensus on the issue that environmentally realistic concentration synergies are not frequent. What 'not frequent' means here is a good question.

Lisette VAN VLIET

It is important to note that three of the major European agencies have sponsored the conference and brought together all the work that has been done so far and I would like these agencies to persuade the European Commission to bring forward an active proposal for advancing the assessment of mixtures in more than just pesticides and a few other places. We need this to go across the board and that will not only help to ensure that in the existing legislation we have better implementation but will also help to start dealing with the gaps.

Timothy BOWMER

My hope is that when we meet again in 10 years' time there will be considerably less of the really dangerous chemicals on the market in mixtures and if we monitor carefully, we will see a difference.

Stefan SCHEUER

Thank you. That was an exciting round of discussions.

Participant

Thank you to Stefan and everyone who participated in the roundtable discussion. It is now my pleasure to introduce Jean-Marie Durand, Deputy Director at the Directorate for Prevention in the Ministry of Ecology, who will make some closing remarks.