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Scientific Steering Committee

STRATEGIES FOR DEALING WITH EMERGING AND RE-EMERGING SCIENTIFIC ISSUES THAT HAVE THE POTENTIAL TO IMPACT HUMAN HEALTH, DIRECTLY OR MEDIATED THROUGH THE ENVIRONMENT

OPINION ADOPTED BY THE SCIENTIFIC STEERING COMMITTEE

AT ITS MEETING OF 26-27 OCTOBER 2000

(Text subject to editorial changes)

STRATEGIES FOR DEALING WITH EMERGING AND RE-EMERGING SCIENTIFIC ISSUES THAT HAVE THE POTENTIAL TO IMPACT HUMAN HEALTH, DIRECTLY OR MEDIATED THROUGH THE ENVIRONMENT[1]

BACKGROUND

An emerging health issue may be defined as one that is growing quite quickly in importance, or is highly likely to do so. This growth in importance may be due to recent evidence indicating a potential adverse effect on human health directly or via the environment, new developments in scientific understanding in a particular area, changed human behaviour and / or escalation of a specific public concern. It is also the case that for these reasons, some known issues can "re-emerge" in a different way.

There are many elements that impact directly or indirectly human health. In incomplete list of elements that contribute to the emergence of new issues is:

- As a consequence of both increasing rapid globalisation, national boundaries are more and more less effective in containing the spread of hazardous materials.
- Increasing urban population density, travel and migration, changing human behaviour, conflicts, etc., resulting in an increasing potential for transfer of chemical, physical and biological hazards or agents.
- Growth in the technological complexity of society leading to increased potential for coupling between risk sources.
- Implementation of new industrial and medical technologies, (including of medical technologies).
- Ability of certain agents to benefit of ecological changes introduced by the previous factors.

Often emerging health issues have not been properly anticipated. As a consequence, risk managers and politicians have been ill prepared to take timely and appropriate action to prevent or minimise their impacts. Public concern has, in the past few years, become a very important factor in identifying emerging health issues. Perceived failure of risk managers and/or politicians to address these concerns effectively can lead to an escalating level of unsubstantiated public anxiety. As a consequence, emerging issues may divert a disproportionate amount of the limited resources and other resources available for public health improvements.

It is important that a formal framework preferably as a tiered system is in place to determine how to deal with uncertainty in the risk assessment process and to balance benefit against risk.

It is against the above background that the Scientific Steering Committee (SSC) has formulated the present opinion, which only deals with progressing issues, not with established risks.

[1] Similar strategies should be developed for other issues such as the environment, animal health, animal welfare, etc.

OPINION

REQUIREMENTS FOR DEALING WITH EMERGING AND RE-EMERGING SCIENTIFIC ISSUES THAT HAVE THE POTENTIAL TO IMPACT HUMAN HEALTH, DIRECTLY OR MEDIATED THROUGH THE ENVIRONMENT

Ideally a balance should be established between encouraging innovations with high potential societal benefits on the one hand and not exposing the public and / or environment to significant involuntary risks on the other. Important requisites for dealing with emerging issues are as follows (A-E):

A) EARLY IDENTIFICATION AND ASSESSMENT AS PART OF THE ESTABLISHMENT OF A RISK PROFILE

It is likely to be the case that if emerging risk issues can be anticipated at a very early stage, appropriate preventative, remediative or minimising measures can be developed before these issues make a major impact.

There are several instances where the form of emerging issues probably could not have been foreseen in advance, e.g.: BSE/vCJD and AIDS. No procedure, can guarantee that every emerging issue will be correctly recognised at an early stage.

An effective mechanism needs to be established (risk factor forecasting) to identify health issues which have yet to emerge. Risk forecasting should include a structured and timely scientific debate on the generic health implication issues associated with important new policies/technology and/or regular brainstorming sessions among experts in public health and related areas on possible scenarios drawing on a knowledge of technical issues, history and changes in social values and concerns. A combination of these measures should encourage constructive analysis of potential implication for human health. As indicated above, it is appropriate to establish a structured evaluation mechanism at an early stage in a likely major and/or novel technological development, when a major change in policy, human behaviour or environmental conditions takes place.

Since there will be many potential emerging issues, a judgement has to be made on which should be given priority. The main aspects to be taken into account for this priority setting are the potential health impact in terms of area/number of the population who might be affected and the seriousness of the health effects (e.g.: life threatening, reversible, irreversible, unsustainable, etc.). Missing knowledge to reach a judgement on the risk may impose a serious limitation to assess the importance of an emerging issue and needs to be addressed as a priority. A proposal for the procedure for the SSC in risk factor forecasting is outlined in Appendix 1.

The SSC has started work on establishing a list of emerging and re-emerging scientific issues that have the potential to impact human health, directly or mediated through the environment. A preliminary list is given in Appendix 2. This list is not final and needs to be updated on a continuous basis. A preliminary and incomplete exploration of several of Appendix 2 was prepared by individual SSC members and is provided in Appendix 3.

B) EFFECTIVE DIALOGUE WITH STAKEHOLDERS

It must be recognised that information of the public in scientific matters is insufficient on its own to allay public concerns about risks to health from various sources. A two way dialogue is necessary, based on a recognition of the legitimacy of public inputs and concerns. Priority needs to be given in the EU to developing mechanisms to achieve this dialogue and utilising it to ensure progress. This includes a more transparent interaction between Scientific Committees and officials. There is, not infrequently, a difference between the perception of risks and the realities of those risks as evaluated by scientific experts. However, even though, in the opinion of scientists, public anxiety over a particular issue is seriously misplaced, it nonetheless needs to be treated seriously, in a transparent manner and with the appropriate scientific effort and stakeholder discussions. It must be recognised that public concern, for instance over the rapid introduction of new technologies (often referred to as the "dread" factor) is likely to be a particular area where a major discrepancy in views regarding safety is to be expected.

Public concern can have a major impact on how an emerging issue is dealt with and the resources that have to be set aside to tackle it.

In order to increase public confidence, the provision of transparent, expert and honest opinion is essential. It cannot be denied that there may be some lack of confidence in scientific advice. For example, surveys indicate that consumers consider the most reliable sources of information in the area of biotechnology to be consumer organisations, environmental protection organisations and only then schools and universities. This is due to many factors including the complex language used by many experts, their apparent lack of interest to explain their views, the variations in approach used for dealing with uncertainties and the absence of evidence and the high profile sometimes given to extreme views by the media.

Means must be found to achieve a regular constructive dialogue between members of scientific committees and the various stakeholders if this situation is to be improved. Possible steps which might be debated to be taken include one or more of the following:

- The publication of a user friendly annual report by each scientific committee;
- Regular meetings of committee representatives with the appropriate European Parliament Committees;
- Stakeholder seminars/workshops on key emerging issues;
- Stakeholder members or observers on some or all scientific committee meetings;
- Regular press briefings for the major periodicals.
- Transparency in the development of opinions, including their pre-publication for comments by modern IT means.
- Auditing of selected opinions[2].

[2] This might evaluate clarity, consistency with previous assessments, scientific data used and the weighting given to it. A retrospective assessment might allow a comparison with subsequent

Further discussions are required to identify which of these (or other options) are appropriate.

C) ESTABLISHMENT OF SURVEILLANCE AND COPING STRATEGIES

In cases where the risk is deemed high in terms of potential seriousness of effect or numbers of individuals/environmental areas that might be affected, a remediation / preventive and surveillance programme can be put in place at the point at which significant public or environmental exposure is recognised as possible. Where applicable, it may be appropriate to limit the extent of use of the risk source while this programme is conducted. This strategy is already in use for human drugs but very rarely for other products to which humans and the environment are exposed.

Priority may need to be given to the conduct of independent research to investigate the actual impacts. Frequently a key aspect of the programme is reliable determination of actual human and/or environmental exposure levels.

Finally, means need to be found to co-ordinate information on the impacts of particular novel technologies at the international level. This is particularly important where the knowledge base is expanding rapidly.

D) STRATEGIES FOR DEALING WITH UNCERTAINTIES AND HARMONISING APPROACHES

i) Dealing with uncertainties

In order to facilitate a reduction in the number of unjustified apprehensions the Scientific Committees need a more consistent approach in particular on how to deal with uncertainties. Whenever it has to be stated, that any speculated risk cannot be scientifically excluded, an assessment of the degree of uncertainty should be made and measures should be taken to clarify the situation. If it is not dealt with objectively, public uncertainties and fears will increase. Dealing with emerging issues only retrospectively is not a responsible approach.

Over-stringent requirements for evidence of safety will stifle development of vital technologies and innovations. In spite of severe constraints, there is a need to find a balance between the requirement for time for further analyses before using a new technology (pre-market) and taking advantage of its opportunities and dealing with safety problems in parallel or subsequently (post-market).

In complex issues there are invariably many questions raised by the public, politicians and academics with different degrees of substantiation and relevance. In order to systematically deal with these it may be helpful to distinguish between risks which are speculative and those which are hypothetical, assumed or real. Of special importance is the handling of those ethical and moral aspects which may influence opinions on areas like animal

information on the actual risk. Comparison of opinions and the basis for these, with those carried out by international bodies such as WHO or in different countries might also be informative.

well fare and GMO. A growing issue is how to demonstrate the quality and transparency of this process.

Since *speculations* are manifold, a transparent and objective procedure has to be developed to deal with these. On one side, they have to be taken seriously if there is public concern, on the other side, dealing with them in depth would be resource inefficient. To develop this procedure in a well balanced way is a major challenge. For *hypothetical* risks, which means that there is some scientific evidence for their existence, it should be possible to develop a clear strategy for their verification or falsification. Clear scientific hypotheses inevitably need to be dealt with comprehensively whenever they claim relevant health or severe environmental impacts. Upon verification of a *hypothetical* risk it will be an *assumed* risk which upon further quantitative information will be identified as *real* and be subject to a full risk assessment.

From a practical standpoint it would not only be appropriate to categorise emerging issues according the previously mentioned criteria, but also to divide them into new issues, re-emerging issues and those where although the issues are not new there is insufficient information available to discount them at present. It is appropriate to avoid a large list of emerging issues whose status remains the same for many years because science is unable to resolve whether or not a significant health risk is involved. It is important to develop a transparent means of defining uncertainties. Further discussion is needed on the scientific input required for the application, where appropriate, of the precautionary principle.

ii) Expert judgement: development of an optimal opinion

Complete scientific information for an unequivocal quantitative error-free risk assessment is probably unattainable. The objective therefore can only be to make best use of available information, or, in some cases conclude that the available information is insufficient for any assessment. It is necessary to update regularly risk assessments where there is relevant new information. Most questions are of an interdisciplinary character or are even intersectorial. (See also the Statement of the SSC of 26.05.00 on *Scientific advice to the Commission from its scientific committees* and the SSC opinion of 27.10.00 on the *Harmonisation of Risk Assessment Procedures.)*

E PROPOSED ACTIONS

It is proposed to introduce a regular review or watching brief on emerging health issues as a formal part of the brief of a multidisciplinary committee such as the SSC. To enable this role to be fulfilled for the SSC, the procedure outline in Appendix 1 could be implemented.

A discussion forum should be held on approaches for describing and characterising emerging and re-emerging scientific issues that have the potential to impact public health.

APPENDIX 1: Proposed procedure for the SSC to address progressing emerging issues

By definition "emerging" issues are likely to be quite quickly developing and cannot be addressed on the basis of a "mature" science alone.

From a procedural viewpoint two groups of emerging issues must be distinguished based on the rate of emergence: urgent and progressing ones. This appendix only deals with progressing issues. Urgent ones are being dealt with by separate procedures and/or by appropriate forums such as the EU's Rapid Alert System (RAS), the WHO, the OIE, etc.

Emerging issues should be a standing item on the agenda of the SSC to enable any emerging issues deemed by any member to be urgent to be identified. Where the SSC concludes that an issue is urgent it should immediately establish a small working party to report back within a defined time period. This report should identify the underlying science, the important gaps in the science base and scenarios for the human and environmental health consequences.

For progressing issues a three-stage process is proposed.

Stage 1:

Summaries should be produced / updated on each topic identified / sponsored by a member of the SSC as falling within the category of an "emerging issues". The summary should be in the form of a standardised format to aid ease of preparation, comparisons and transparency. Such summaries would typically be produced by members of the SSC, but it could be acceptable for others to generate an emerging issue summary too, provided a member of the SSC is willing to act as its "sponsor". It should be noted that Appendix 3 is not a list of such summaries, but only a preliminary and incomplete exploration of a number of items drafted by individual SSC members. Chairmen of the scientific expert committees would normally act as sponsors of a summary produced by a member of their Committee, but may produce a proposal in their own competence.

At least once per year a specific meeting of the SSC should be set aside for the brainstorming on possible future issues and review of all summaries to rank priorities (high, medium or low) for the development of discussion papers (see Stage 2 below). In establishing priorities the SSC should try to set them in the context of risks from established sources. It may be appropriate to invite various stakeholders to participate in part or all of such meetings. The meeting might also include a seminar on a specific emerging issue. The summaries of all emerging issues, once seen and agreed by the SSC, should be readily accessible on the Internet. (Consideration should be given to providing both technical and non-technical summaries where the issue is technically complex).

Stage 2:

Emerging issues, identified as a high priority by the SSC, should be developed as "discussion papers". Typically, a discussion paper will be generated by a small working party (chaired by the SSC author/sponsor of the Stage 1 summary. As for other SSC working parties, it should draw upon expertise from the appropriate DG SANCO Scientific Committees plus, where needed, external experts. Opportunities

for links with other international groups working on the topic should be sought wherever appropriate.

Discussion papers need to take a broad approach to the topic. There must be allowance made for informed speculation. On-going research should be identified and areas flagged where additional information is sought and is not covered by on-going research. It is essential, at the discussion paper stage, that members of working parties do not adopt a defensive posture, either in terms of how the scientific committees have tackled such issues in the past, nor using the argument that there is insufficient evidence and therefore an aspect cannot be commented on. The degree of uncertainty should wherever possible be characterised clearly. Following consideration by the working group of these comments the discussion paper should be modified as appropriate.

Once a discussion paper has been agreed by the SSC, it should be available on the Internet for comments for a number of weeks. This should be followed by a stakeholder forum (which could include representatives of other international bodies working on the same topic) at which there is a thorough debate on the modified discussion paper and on opportunities for further refinements stemming from it.

Stage 3:

The modified discussion paper, the proceedings of the stakeholder forum and discussions with EU member state officials with a particular involvement in the topic, would form the basis for the development, by the original working group, or possibly by the group with additional members, of a "position paper" to be adopted eventually by the SSC. "Position papers" will need to be clearly dated and should include clear recommendations for both short term and longer term research. [NB: Discussions should be held with DG Research regarding the most appropriate point to involve them in the development of the position papers].

APPENDIX 2: Preliminary list of emerging and re-emerging scientific issues that have the potential to impact human health, as identified by <u>individual</u> SSC members✪

(A number of the items listed in this Appendix are further explored in Appendix 3)

ITEM
1. AGENTS
a) Infectious agents (including genetically modified agents and crossing the species barrier).
b) Natural toxins
c) Antibiotic resistant micro-organisms (including new infections because of antimicrobial resistance and/or because of increased virulence of agents)
d) Nutrient imbalances (both micro- and macro) and their direct and indirect consequences for disease
e) Industrial chemicals in the environment (including non communicable chronic diseases, causes and prevention: role of industrial chemical and chemical pollutants from food and environment)
f) Gene therapy; safety of vectors used in gene therapies
g) Bioterrorism
2. MEDIA
a) Drinking water: quality and quantity
b) Air quality
c) recycling of toxic substances (including new processes of waste treatment and recycling animal waste)
d) Radio frequency (RF) fields and Electro-magnetic (EM) fields
3. MEDIA FOR TRANSMISSION
a) Blood transfusions (including upcoming diseases due to blood transfusion
b) Xenotransplants
4. PARTICULAR EFFECTS OF CONCERN
a) Endocrine disruption (human and environmental) (including environmental pollutants and endocrine disrupters and their interference with the immunosystem)
b) Allergenicity
c) Climate change

✪ This list is not intended to be fully comprehensive. It should be considered to be the result of a brainstorming. It is not ranked in terms of priority or in any other way. The SSC stresses that it is in no way to be considered as list of priority public health concerns. Many other, and in many cases more important, public health and consumer protection issues do not figure on the list, for example because they are being addressed already, because they are not a "possibly emerging risk", because they are not within the mandate of the SSC, etc.

APPENDIX 3: Preliminary exploration of a number of emerging and re-emerging scientific issues that have the potential to impact human health, directly or mediated through the environment.

It should be noted that this Appendix 3 is not a list of such summaries as referred to in Appendix 1, but only a preliminary and incomplete exploration of a number of items drafted by individual SSC members.

1) AGENTS

a) Infectious diseases

Summary of the issue

The control of emerging infectious diseases, as in the past, will most likely be a severe challenge also in the near and long term future. In the following those scenarios that can be foreseen have been exemplified. In spite outbreaks of infectious diseases often have a multifactorial cause which we in many cases simply do not know an attempt has been done to classify those examples according to their main principal cause of origin.

Reintroduction

By far the most appealing achievement of modern medicine has been the world- wide eradication of smallpox in the late 1970's. This was the result of an unprecedented international collaborative effort, co-ordinated by the WHO, using the first live attenuated vaccine that had been introduced about two centuries earlier by Jenner. Similarly, considerable progress has been made with the world- wide eradication of poliomyelitis, which is expected to be finalised within the coming years. Also a start has been made with the eradication of measles, which has now virtually disappeared from the Americas. Corresponding efforts have since long eradicated or controlled the most important epizootic diseases, e.g. foot and mouth disease and African and classical swine fever from the animal production of all or most of the countries of the western hemisphere including the EU.

However, the current relatively good status achieved of control of many of the most serious pathogens is threatened due to uncontrolled reintroduction of pathogens e.g. by refugees and other migration of people and new pattern for trade of animal and animal products. The reoccurrence in EU and other developed countries of human tuberculosis because of immigrants is one example. In animals the epizootic of classical swine fever in the EU during the 1990-ies demonstrates how epizootics of well-controlled diseases suddenly can occur and easily be spread between countries as a result of trade. The cost for such epizootics is often very substantial. As an example the cost for the classical swine fever epizootic in the Netherlands 1997-1998 was estimated to 2.5 billion ECU.

In this respect it should also be considered that the political ambition to obtain also on global base, a free trade is in conflict with the control of animal and human infectious diseases in individual countries or regions. This can lead to a situation where the lowest animal health status of participating countries is considered as the standard leading to a threat to animal and human health in countries with currently a higher health status.

New technology in animal- and food production

Technical interventions and improvement of animal production have historically resulted in problems like the dramatic spread of bovine tuberculosis to humans and animals by unpasteurized milk delivered from the increasing dairy industries some 70 years ago. A current and striking example is the ongoing BSE (bovine spongiform encephalopathy) epizootic which primarily emerged as a result of a technical change of the rendering process. A batch wise process under high temperature and pressure was replaced by a continuos one running at lower temperature without pressure. The new process in contrast to the previous one could not inactivate those prions that are the cause of BSE. The agent, when present could therefore be propagated in animals by feeding them prion contaminated meat and bone meal. Subsequently humans were also infected resulting in the emerging of a new variant of Creutzfeldt Jacob disease (vCJD) which has so far caused the deaths of approximately 80 individuals. In addition 180 000 cattle have so far died from BSE. The need for continuous awareness on possible side effects of the introduction of new technical processes can be foreseen.

New medical technology

Also newly emerging medical techniques, like blood transfusion, vaccinations, transplantation of organs or tissues between humans (allotransplantation) or between animals and humans (xenotransplantation) may easily, if performed without the necessary precautionary measures, contribute to the emergence of virus infections in humans and animals. The spread of infections by vaccines and blood transfusion can easily be exemplified. Currently safe methods for xenotransplantation is especially focused and therefore dealt with separately in this document.

Intervention on wild animal ecology

Interventions in the ecology of the wild animal fauna can lead to dramatic and unforeseen zoonotic and environmental implications. Such a change was seen when the fox population in the Scandinavian countries in the 1970-thies practically was wiped out due to mange leading to a dramatic change in the ecology of the wild animal fauna when the fox being the main predatory animal disappeared. The opposite situation is currently seen on the European continent when the sylvatic fox rabies nearly is eradicated by vaccination. Attempt to keep the fox population down is no longer needed and the number of foxes are increasing accordingly. So has the shedding of their tapeworm Echinococcus multilocularis that via berries and mushrooms infect humans leading to serious and lethal damages of the liver. It can be assumed that this disease already is causing more human deaths that previously were caused by rabies. In addition the traditionally free human access to the nature can be limited.

Climate changes

Environmental disturbances can lead to similar problems even if the causal aetiology often is not fully understood like the epizootic of “canine distemper” in seals in the water round Northwest Europe some years ago. A whole range of not previously undiscovered morbilliviruses was identified as the primary cause of mass mortalities in aquatic mammals like seals and dolphins. The epidemic that killed about 50% of the total harbour seal population of north-western Europe in the late 1980’s was

caused by the introduction of a “new” morbillivirus: phocine distemper virus (PDV). Probably due to the profound immune suppression that infection with this virus caused, a plethora of other viruses was isolated from affected animals.

Two years after that outbreak, mass mortality was observed also among striped dolphins in the Mediterranean Sea. The primary cause was again, a not previously discovered morbillivirus: dolphin morbillivirus (DMV). This virus proved to be closely related to a virus that was discovered previously as the cause of mortality in porpoises: porpoise morbillivirus (PMV). Subsequently a DMV-like virus was discovered in highly endangered Mediterranean monk seals that had died off the coast of Mauritania and in Greek waters . Interestingly, a similar disease outbreak that occurred among Baikal seals in the Lake Baikal at approximately the same time was caused by the interspecies transmission of canine distemper virus (CDV) from local domestic dogs .

The heavily polluted coastal waters, has lingered concerns that persistent organic pollutants (POPs), many of which are demonstrated immunotoxicants, including PCBs, dioxins and furans, played a contributory role to these mass mortalities in rendering the animals more susceptible to the effects of these infections. Experimental studies have supported that theory.

The mass mortality of seals described above should primary also be seen as an outbreak of an infectious disease, when the agent is introduced in a fully susceptible often isolated population. This is described for several infections including canine distemper e.g. when a large part of the dog population of Greenland was killed as a result of the introduction of the CDV. The example thus also clearly exemplifies how large epidemic can be foreseen when earlier eradicated agents are reintroduced as focused above.

Immunotoxicity, increased susceptibility to infections, and top predators

While many factors, both intrinsic and extrinsic, affect the immune system of wildlife species, chemicals arising from human activities present an additional concern. Bioaccumulation in the food chain results in high concentrations of many of the lipophilic polyhalogenated aromatic hydrocarbons (PHAHs) as contaminants in organisms occupying high trophic levels. Consistent with this, most of the biological effects of such contaminants have been observed in top predators, and organisms of particular concern include the piscivorous birds, seals, dolphins and whales.

Climate changes and unconventional contact between animal species

The green house effect is considered to be a contributing factor e.g. to the violent forest fires in Australia and surrounding islands wish resulted in migration of fruit bat colonies (flying foxes) to new locations. When in close contacts to pig productions previously unknown zoonotic diseases occurred. This was because the bats often were the reservoirs not only for rabies virus but frequently also for different types of paramyxoviruses like the Nipa virus (Malaysia) and Hendra and Menagle viruses (Australia). These were transmitted to pigs and subsequently a fast spread occurred between pig with spill over also other animal species and in contact humans. In last months of 1998 and early 1999 a severe Nipa virus epidemic occurred in Peninsular Malaysia and Singapore with secondary spread to humans. In Malaysia there were in excess of 265 cases with 105 human deaths recorded during that period. More than 1

million of pigs were destroyed with the purpose of eradicating the infection. Severe neurlogical and respiratory signs characterised the disease both in animals and humans. These viruses can most likely be introduced also to Europe. One reason is that the fruit bats in spite being the virus reservoir can hardly be controlled because it is protected in most countries like Australia.

Humane contact to primate virus reservoir

The increase of contacts between humans and wild or feral animals due to e.g. changing habitats or climatological conditions may directly or indirectly lead to the emergence of virus infections in humans. The close relatedness between humans and primates allows many viruses to cross the species barrier between the two. Besides the introduction of HIV-1 and HIV-2 into the human species, many other primate viruses have caused major problems in humans: Outbreaks of monkey pox and filovirus infections are recent examples that have attracted considerable media attention. The ongoing identification of not previously recognised retro-, hepadna- and herpes viruses, which all proved to be closely related to human viruses of the same virus families, illustrates the existence of virtually unlimited primate reservoirs of potential human pathogens. Contacts of humans with wild rodent populations that have increased due to climatological changes may also lead to severe outbreaks of virus infections like the recent Hantavirus infections with high case fatality rates in the Americas.

Insect borne infections

A change of the epidemiology resulting in dissemination of vector borne infections is often observed following climate or environmental changes. The increased distribution of arthropods like *Aedes aegypti* has led to massive outbreaks of Dengue virus infection with high mortality rates due to dengue haemorrhagic fever and dengue shock syndrome in middle America and south-east Asia. Recently, another flavivirus transmitted by mosquitoes, West Nile virus, was introduced in North America where it caused outbreaks of encephalitis among inhabitants of New York and New Jersey. The virus was introduced into avian reservoirs about one year ago.

In the animal sector there is a constant risk for the spread of insect borne infections from Africa which can be established in the southern parts of Europe as have been seen for African Swine fever and African Horse sickness.

Pathogens resistant to antimicrobials

The ongoing increasing problem with antibiotic resistance can also be foreseen to end up in situations when antibiotics no longer can treat bacterial infections. The increasing problems with human tuberculosis caused by multiresistant strains is currently one example as is the fast spread of Salmonella DT 104 which have been found to be resistant against up to nine different antibiotics. Another is the multi resistant strain of Mycobacterium tuberculosis causing severe problems with human tuberculosis in New York as is also seen in the EU in immigrants from Eastern Europé. The resistance against antiparasitic drugs may also lead to situations that have to be focused.

Genetic modification of microbes

The continuously ongoing adaptation and genetic changes of microbes can as before easily lead to emerging of infectious diseases. The antigenic shift and drift is typically well known in strains of influenza virus. This repeatedly and often annually result in new pandepidemic waves of influenza in humans. Here again is an example where contact and exchange of viruses between different animal species and humans is an important part of the complex influenza epidemiology.

Birds play an important role in the epidemiology of influenza of humans. In the past century, three major influenza pandemics resulted in the loss of many millions of lives. The Spanish flu alone caused the deaths of more than 20 million people by the end of the first world war, which itself, due to war activities resulted in about eight million deaths. After the introduction of a new pandemic influenza A virus from an avian reservoir, influenza A viruses have been shown to continue their circulation, which eventually leads to more deaths than those during the initial pandemic outbreaks. Probably, after introduction of an influenza A virus from an avian reservoir into a mammalian species, the virus needs to reassort with an existing mammalian influenza A virus, to become a real pandemic virus. After the recent episode of the H_5N_1 so-called chicken influenza virus outbreak in Hong Kong (2,3), in which six people died, it became clear that such a reassortment event could probably also take place in humans (4). It is quite likely that influenza pandemics will also occur in the next century. It is, however, impossible to predict when this will happen and which influenza A virus will be involved. Any predictions in influenza epidemiology seem to be spurious

Genetic modification naturally occurs also in bacteria. The ability of Salmonella enteritidis to infect the inside of the egg of the hen and in very low doses infect both animals and humans was suddenly seen ten years ago. That resulted in a world- wide spread, a true pandemic, in both animals and humans and was a main reason to the establishment of the zoonoses directive of EU. If that strain of salmonella also had been resistant to significant antibiotics the problems would have been even more serious. Similar changes in the virulence can always be foreseen.

New viruses

Finally, previously unknown pathogens especially viruses regularly evoke in both animals and humans. HIV and influenza are today probably the most serious example. From the animal sector canine parvovirus in dogs and PRRS in swine are two examples, which during the last 15 years has resulted in a worldwide spread to become diseases of significant economic importance.

It thus seems paradoxical, that at a time that we are capable of eradicating virus infections which over the centuries have killed millions of people and have severely wrecked the lives of many millions more, we are apparently confronted with several new or newly emerging virus infections of man and animals. Especially in the last decade many new virus infections seem to have emerged. The obvious question is, whether this observed increase is indeed real, or is the result of an increasing attention and diagnostic knowledge. The major changes that may have contributed to, or predisposed for this apparent increase, are related to changes in human behaviour, increase in human mobility, demographic changes, human exploitation of the environment, decreased attention for infectious disease research, education and control and the ability of certain viruses to rapidly adapt to a changing environment.

In fact all these predisposing factors have largely contributed to the world- wide spread of HIV-1 and HIV-2 from primate reservoirs in the last two decades. Especially for these two viruses, changing mores and taboos, intravenous drug abuse, travel, wars, increase in population density and urbanisation, contacts with wild primates, breakdown of public health infrastructure with loss of expertise and the extreme variability of these viruses, all have contributed to the currently ongoing sever and tragic human pandemic of AIDS. The AIDS and BSE clearly demonstrate the urgent need not only to handle the current problems but merely as much as possible to prevent future threats to human and animal health caused by epidemics of infectious diseases.

In conclusion it may be stated that during the past decades, a complex mix of social, technological, ecological and viral changes has predisposed for the emergence or re-emergence of virus infection in man and animals after they had crossed species barriers. The establishment of well-coordinate national and international surveillance networks, as well as the development of novel vaccine- and antiviral development strategies should provide the safeguards to limit their impact in the coming century.

Current status and assessment of risk

It is probably impossible to estimate the magnitude and importance of possible future epidemics of the infectious diseases. Their course is dependent on actions undertaken for prevention and control. The ongoing BSE –epidemic emphasise those proportions and cost to which an epidemic can reach, as did the pandemic by Salmonella enteritidis in the 1980-ies. It was estimated that in one member state (Germany) 2 million people annually were sick due to salmonella infections out of which 2000 died. Another example is that in Sweden annually 800 deaths are caused by hospitaly acquired infections from those 100 000 found to become infected.

Globally by WHO and OIE, in the EU as in individual countries different organisatory bodies and routines are in place to follow and take necessary actions in case of occurring severe epidemics. In the EU this is well organized for the A-listed epizoootic diseases of the animal production. However, for remaining animal and zoonotic diseases as generally for the corresponding infectious diseases affecting humans as for their possible environmental impact much less stringent routines are in place. Of basic importance for the allocation of recourses and implementation of preventative actions are the establishment of effective systems for surveillance of disease occurrence and the need for the assessment of the current situation and possible future risks involved.

Need for risk assessment by the SSC

Assess the current situation for the importance of prevailing infectious diseases. Certainly a lot of data is existing but they have to be collected evaluated and if necessary additional studies have to be performed.

Assess the existing surveillance, communication between member states as well as third countries as a base for assess risks involved with emerging infectious diseases.

For SSC it is of special importance to follow up the risks involved with antibiotic resistance as a follow up of its previous opinion and recommendations on this issue.

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b) Natural toxins

It is well known that plants contain chemicals of natural origin that have poisonous, medical, stimulatory, hallucinatory or narcotic effects (NRC, 1996). In the human diet the number of naturally occurring compounds is far greater than that of synthetic compounds and it includes many toxins. In traditional food safety assessment for these toxins the concept of "safety in numbers" has been accepted.

More and more stringent regulatory requirements for chemicals used in animal/plant production and food technology and a growth public belief that "natural" equates with "safe" have led to the alternative use of plant extracts (antioxidants, immunostimulants, health protectors, aromas) which are not included in the existing regulatory frames or only submitted to very light requirements. These extracts are freely sold (health shops, internet) as food supplements through nutritional allegations highlighting their protective effects against different human pathologies (nutracetics).

Paradoxically, synthetic compounds have as yet received much more attention as to their toxicity and safety. The above mentioned NRC report concludes that where the great majority of naturally occurring chemicals in the diet appears to be present at levels below which any significant adverse biological effect is likely, natural components of the diet are often present in much higher quantities and therefore of greater concern than synthetic ones

Certainly some natural chemicals (such as alkaloïds, phytoalexins, mycotoxins, goitrogens, phyto-estrogens, furanocoumarins, seafood toxins and the like) may pose a risk to humans. The tendency to increase our diet with more vegetables and fruit, to use more herbs, to buy plant extracts and to consume functional foods (nutracetics) may in conjunction with the established beneficial effect on health, also lead to intakes of natural chemicals in quantities which may be harmful. The same risk may result from the consumption of vegetable, fruit or herbs genetically modified to increase the contents of these natural compounds, as well as from an eventual pleiotropic effect of the introduced genes that would over express genes coding for the corresponding metabolic pathways. It, therefore, is a necessity to elucidate better and more precise the roles naturally occurring substances may play in disease causation and prevention and to develop strategies for selection of natural substances for toxicity testing and risk assessment.

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Current status

For certain identified mycotoxins such as aflavotoxin ß risk assessments have been made by international authorities (JECFA, WHO/FAO). Other mycotoxins like ochrotoxins and finosoril are under evaluation. In these cases one may speak of real risks. For most natural substances however, it is simply not known if they bear a risk

or not, due to insufficient data available, therefore one only can speak of a hypothetical risk affecting probably large sub-sets of the population.

Assessment of the risk

Certain mycotoxins do occur quite universally so they may reach a large part of the population, though usually in small quantities. Also for natural substances as yet not known or of which a negative/adverse effect is not known to occur, it is likely that they reach a considerable part of the total population. Effects may vary from light to severe and will usually occur after a considerable latency period.

Need for a Risk Assessment for the SSC

Certainly for a number of natural occurring substances, information is available, but there exists a need to group the information tests and to produce integrated documents for evaluation. Additionally exposure patterns should be evaluated and exposure characterisation should be improved in order to assess eventual risks and benefits. Intermediate to high priority.

c) Antibiotic resistant micro-organisms (including new infections because of antimicrobial resistance and/or because of increased virulence of agents)

d) Macro- and micro-nutrient imbalance and its direct and indirect consequences for disease

e) Industrial chemicals in the environment (including non communicable chronic diseases, causes and prevention: role of industrial chemical and chemical pollutants from food and environment)

f) Gene therapy: safety of vectors used in gene therapies

Summary of the Issue

Public awareness of the use of genetic material as a scientific approach to innovation in many areas that effect every day life such as food, medicines and pollution has produced different reactions. Whilst people recognise the potential benefits, they also have fears about potential risks from unknown effects of introducing genetic material, particularly genetically modified organisms, into the environment. In the area of medicines, gene therapy researchers are using modified viruses as vectors to insert human genes into specific target cells to try to influence the course of human diseases such as cancer, AIDS, cardiovascular disease and monogenetic disorders.

Successful gene transfer and expression in a target cell can be achieved by two general categories of delivery vectors/vehicles. One uses DNA and RNA viruses as vectors, the other delivers bacterial plasmid DNA either by direct injection, or complexed with polylysine, cationic lipids and/or cell-receptor ligands. Of the two categories the genetically modified viral vectors are more likely to raise safety

concerns with the public because they can potentially be released into the environment and cause widespread infection.

Despite more than a decade of research relatively few suitable viral vectors systems are available for use in humans. Current recombinant viral vector designs usually include biological containment. That is the foreign (therapeutic) gene sequences along with the requisite regulatory sequences for expression are incorporated into the genome of a parent replication-deficient virus. These viruses can only be propagated in packaging cell lines genetically modified to express the viral proteins necessary for the production and packaging of viral genomes containing the foreign gene to be transduced.

The main hazard associated with this technique is the potential for a replication-deficient virus to reacquire the ability to replicate by combining with, or complimenting viral nucleic acid sequences that may contaminate the propagating system or by recombination with endogenous viral sequences in production cell substrates. The potential hazards from release of a replication competent genetically modified organism into the environment depend on the type of virus and the genetic modification.

For retroviruses major safety concerns include the potential to integrate randomly into host cell DNA and activate oncogenes or inactivate tumour suppressor genes leading to cancer. The potential to combine with endogenous viral sequences to create a pathogenic virus could cause a serious infection that may spread in the community. Adenoviral vectors can mount immune responses including humoral and cellular responses in patients but the potential biosafety hazard is likely to come from the pathogenicity of the parental vector and/or pathogenicity of a replication-deficient viral vector that has regained the ability to replicate through recombination. The safety aspects of herpes simplex virus which have a propensity for transducing neuronal cells are as yet not well described. However, concerns have been raised about the possibility of a pathogenic virus replicating in the central nervous system when used to treat brain tumours. The latency and persistence of the virus in neural tissue after initial contact and its ability to be reactivated could complicate its safe use. Adeno-associated viral vectors require a single-stranded DNA human parvovirus co-infected with adenovirus or herpes virus for propagation. The propagation procedure may be subject to contamination with adenovirus which could allow the introduction of a pathogenic wild-type virus that could infect patients and their contacts. Lentiviral vectors are being developed because of their unusual ability among retroviruses to infect non-dividing cells The safety concerns are similar to retroviruses i.e., the potential to activate oncogenes or inactivate tumour suppressor genes and the potential to create a pathogenic replication-competent virus. Being similar to HIV viruses creates the additional potential for producing a wild-type replication competent retrovirus as a result of complementation with wild-type HIV virus and the potential spread within the community. The ethics of excluding people infected with HIV from treatment with these vectors will have to be considered.

Current Status

Whilst the public and media are very interested in the progress of gene therapy towards new treatments for diseases, government regulators, ethics committees, researchers and the biotechnology industry are taking precautions to try to minimise the risks from the known hazards of viral vectors. The principles and methods of Microbiological Risk Assessment have been studied by a number of expert groups. For a summary see reference[1]. Directives and guidance are in place to minimise the biosafety risks of genetically modified living organisms associated with their contained use[2] and their deliberate release[3] into the environment which might pose risks to the wider human population.

Government regulators, in consultation with advisors, have set out manufacturing methods and controls to minimise the risks of creating a new pathogenic organism. Guidance is available on the philosophy and regulation of biological medicinal products in the EU[4]. This guidance is also applicable to products for clinical trials. Also, recently the Committee for Proprietary Medicinal Products (CPMP) completed the consultation on guidance on the manufacture, pre-clinical testing, and clinical evaluation of products used in gene therapy[5]. It specifically addresses the precautions that must be taken to avoid the creation of a pathogenic organism from a replication-incompetent viral vector.

The risks associated with viral vectors are recognised world-wide. The US, FDA published guidance on Human Somatic Cell Therapy and Gene Therapy (March 30, 1998) and the Japanese MHW published guidance on quality and safety assurance of gene therapy products in November 1995. Because no single comprehensive source of guidance exists, a proposal was submitted to the International Conference on Harmonisation (ICH) in July 2000, to develop an ICH guideline on cellular and gene therapy products. Although the proposal was not accepted, it was agreed that an Expert Working Group be constituted within the structure of the ICH for exchange of information between the three regions.

Assessment of Risk

Currently exposure to gene therapy viral vectors is limited and is almost entirely in research protocols, which include a few trials in the EU and about 300 trials in the US. Most of the trials are for cancer indications, but protocols have been approved for cardiovascular disease and monogenetic disorders. The results are most promising in certain forms of cancer eg, head and neck. If current progress is sustained it could lead to a Marketing Authorisation within 3 to 5 years. Then the exposure of the population would increase significantly.

Need for Risk Assessment by Scientific Steering Committee

The potential risk of release of a pathogenic organism into the environment has been assessed in the EU in preparing and modifying Directives 90/219/EEC[2] and 90/220/EEC[3] on contained use and deliberate release of GMOs and in considering the environmental risk assessment required for marketed medicinal products under Council Regulation 2309/93/EEC[6]. The specific risks for gene therapy viral vectors have also been evaluated by the CPMP and its Biotechnology Working Party. There is probably sufficient data and adequate methods to assess the risks of creating a pathogenic virus from a viral vector and releasing it into the environment. These

could be used assess the potential risk of handling gene therapy products in normal medical practice.

Taking into account the current ongoing evaluations by other groups and the likely time scale before any gene therapy product receives a marketing authorisation in the EU, it is recommended that an intermediate priority is given to the need for risk assessment by the Scientific Steering Committee. However this priority could change if product development led to a medical breakthrough involving widespread use of viral vectors for a common disease. Then it would important to rapidly communicate the evaluation of the risks of using viral vectors as medicinal products in normal medical practice.

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g) immunotoxicity, increased susceptibility to infections, and top predators

While many factors, both intrinsic and extrinsic, affect the immune system of wildlife species, chemicals arising from human activities present an additional concern. Bioaccumulation in the food chain results in high concentrations of many of the lipophilic polyhalogenated aromatic hydrocarbons (PHAHs) as contaminants in organisms occupying high trophic levels. Consistent with this, most of the biological effects of such contaminants have been observed in top predators, and organisms of particular concern include the piscivorous birds, seals, dolphins and whales. Among the broad range of effects on physiological processes, the immune system has been shown to be particularly sensitive to the toxic action of many of these compounds. Earlier studies in several laboratory animal species demonstrated that the bioaccumulating PHAHs and organotin compounds were immunosuppressive and as a consequence increased the susceptibility of the animals to infectious diseases. Results of laboratory or semi-field studies using fish-eating birds and seals have shown that PHAHs indeed pose a great immunotoxic threat to these species.

The mass mortality of harbour seals in northwestern Europe in 1988 resulting from infection with the seal phocid distemper virus led to speculation about the possible

contributing role of environmental contaminant-induced immune suppression. In order to investigate the role of immunotoxic environmental pollutants, a semi-field study was carried out in harbour seals that were fed herring from either the highly contaminated Baltic Sea or the relatively unpolluted Atlantic Ocean. A variety of parameters related to immune function were monitored over a period of 2 year. Natural killer-cell activity and T-cell dependent immune responses were significantly reduced in the Baltic Sea group, indicating that in harbour seals the resistance to a virus infection is impaired. Additional studies implicated the dioxin-like PCBs as causative contaminants. As many free-ranging harbour seal populations inhabiting polluted areas of Europe and North America have PCB blubber concentrations being at or above those observed in the Baltic group of seals of the semi-field study it was further concluded that, in addition to its contribution to the severity and extent of the 1988 morbillivirus outbreak, chemical-induced immunosuppression may affect the immunocompetence of free-ranging populations in many areas of the industrialized world. This is the more true as free-ranging seals are likely to be more vulnerable than the seals of the semi-field study as perinatal TCDD exposure produces more profound immunosuppression, and the lifespan of seals allows for long-lasting accumulation. In this case, the "weight of evidence" from laboratory, semi-field and epidemiological studies highlighted PCBs as a significant threat to the health of seal populations, an approach that should be further pursued to assess in wildlife species the risk of chemical-induced immune suppression.

2. MEDIA

a) Drinking water: quality and quantity

Human survival is certainly dependent on the availability of drinking water of sufficient quality. Outlook scenarios are not optimistic in relation to the availability of sufficient, clean water for man. But even today, daily over 5000 children die from diseases related to water. Microbial diseases do occur in certain areas in the world and are found to be transmitted via drinking water or recreational water. Increased infection pressure is expected in particular to microbial diseases such as typhoid and cholera in Eastern Europe and new diseases like cryptosporidium. Epidemiological studies indicate that ultrafiltration of water reduces gastroenteritis in man by one third. Quantitative risk assessment methodological and mathematical modelling with uncertainty analysis may better predict health outcomes and/or prevent them.

Current status

Insufficient is known about the real impact of emerging, hitherto unknown, microbial (viral) diseases transmitted by recreational or drinking water. Thus, although the risk is hypothetical, if it occurs it may affect a considerable number of people. A known unexpected exacerbation was the outbreak of cryptosporidium in the United States, which was the impetus to the requirement of sterilising drinking water before use.

Assessment of the Risk

Risks involved will likely and primarily affect a vulnerable sub-set of the general population and will be confined to the water reserves supplying a certain area.

Need for a Risk Assessment by the SSC

Insufficient is known about methodologies to detect small quantities of infectious agents (including viruses and virus-like agents such as ------) and to predict their possible impact. Development of Quantitative Risk Assessment procedures in particular for microbes is another necessity. Although an issues of moderate priority, it may be that outbreaks in Europe will change its priority to high.

b) Indoor air quality

Summary of the issue

Individuals of all ages, particularly in the developed world, spend increasing amounts of time in an indoor (enclosed) environment in many cases approaching 100% of their time. Furnishings, cooking and heating facilities, use of cleaning and other domestic products, personal care products, passive tobacco smoke, air conditioning, building insulation and suspended biological material of many kinds are major contributors to air quality.

Current status

Very little is known about the health consequence of indoor air quality. Bearing in mind the large effort dedicated to external (ambient) air quality over the past few decades, this is a serious and surprising omission.

Assessment of the risk implications

The concern stems from the very extensive exposure for a lifetime of virtually the entire population of member states and the very serious inadequacy of the data base to characterise the risk involved except from specific sources. Evaluation might be progressed by establishing a “typical” indoor air quality exposure profile in urban situations. Factors producing major deviations from this profile should be identified. (It is noted that indoor air quality for laboratory animals used for toxicity testing is usually only defined in terms of number of air changes per unit time).

Need for a risk assessment

If air quality is important for human health, then priority should be given to understanding the impact of indoor air quality because risk assessment strategies need to be devised to progress knowledge in this area.

c) Health hazards due to the recycling of toxic substances

Summary of the Issue

The efficient use of resources requires the recycling of wastes at a high level preferably not by combustion. This may lead to a dilemma since simultaneously toxic and hazardous substances present in the waste are also recycled, and thus may re-enter food and feed chains. Respective products are composts from different materials, sewage sludge, manure and liquid manure used as fertilisers. Furthermore the products derived from technologies to handle dead animals and fallen stock, also fall into this category. As regards contaminations, which are recycled, in these products, global hazardous substances, the concentration of which increases in

certain products, have to be considered like heavy metals and persistent organic pollutants (POPs), but also residues from immediate use like e.g. residues of plant protection agents or veterinary medicines.

Current Status

For global persistent hazardous substances, there exist limit values for the recycling of materials, like compost or sewage sludges in agriculture. These are usually derived pragmatically. Nevertheless, upon long-term use of these materials they may result in a slow accumulation, which may lead to possibly non-safe levels of these compounds in food and feed. For specific hazardous substances which may pose a hazard due to their persistence and effects potential, e.g. certain antimicrobial agents and some endocrine modulators, assessments under this aspect do not exist.

Assessment of the Risk

The risks involved in recycling of toxic and hazardous substances are of a long-term nature. The potential health and environmental effects may be considered to increase the total toxics exposure.

Need for a Risk Assessment by the SSC

Since the issue is quite complex and additionally needs to be dealt with in different regulations it is not suggested, that the SSC prepares risk assessments regarding the recycling of specific toxic substances, but takes an overall initiative to assure that unacceptable risks by recycling toxic substances are avoided upon inclusion of this issue in all relevant compound and techniques assessments.

d) Radiofrequency (rf) fields

Summary of the issue

Several studies are in progress to clarify whether radiofrequency fields from mobile phones may affect cancer risk of the users. The results of these studies could be of importance for risk assessment and risk reduction policies following concerns raised by episodic reports on the long term effects of exposure to RF.

Current status

Natural human-made sources generate RF fields of different frequency. Common sources of RF fields include: monitors and video display units (3-30 kHz), AM radio (30kHz – 3 MHz), FM radio (30 – 300 MHz), mobile telephones, television signals, microwave ovens communications (3 – 30 GHz) and the sun (3 – 300 GHz).

Exposure to RF fields may cause heating or induce electrical currents in body tissues. Heating is the primary interaction of RF fields at high frequencies, i.e. above 1 MHz. Below this frequency, the induction of electrical currents in the body is the predominant action of RF exposure.

The brain, parotid gland and acoustic nerve are among the tissues most exposed to radiofrequency energy when a mobile phone is used. In 1997 a meeting was convened by the World Health Organization, the International Commission on Non–ionising Radiation Protection, and the German and Austrian governments in response to public concern that increasing use of mobile phones may harm health.

Population exposures to RF fields generated by telecommunication devices and their health effects are difficult to assess. However, due to the extensive presence in the environment of radio and TV signals as well as telecommunication facilities, including the widespread use of mobile phones, some degree of exposure to this type of electromagnetic field can be considered universal.

Assessment of the Risk

A recent opinion by the SSC and a recent scientific review by WHO, published within the framework of the International EMF Project (WHO International EMF Project. http:// www.who.int/inf-fs/en/fact183.html.1999), concluded that, from scientific literature currently available, there is no convincing evidence that exposure to RF shortens the life span of humans, or induces or promotes cancer. However, the same documents also stressed that further studies are needed to draw a more complete picture of health risks, especially about the possible cancer risks from long-term exposure to low-levels of RF. In order to clarify the extent of the risk, several studies on this issue are in progress including a major investigation by WHO/IARC on central nervous system cancer and exposure to radio frequency fields.

If a risk exists, at the individual level it is likely to be small. However, in view of the large and steadily growing number of mobile phone users, it is important for public health reasons that it be studied.

Need for a Risk Assessment by the SSC

The Scientific Steering Committee adopted on 25-26 June 1998 a report and opinion on possible health effects from exposure to electromagnetic fields (0 Hz – 300 GHz). This opinion should be reconsidered as soon as new data become available.

3. MEDIA FOR TRANSMISSION

a) Blood transfusions

b) Xenotransplantation

Summary of the issue

Advances in medical care have provided effective treatment for many common diseases and resulted in the survival of patients for whom the only effective treatment has become the transplantation of human cells, tissues or organs. There is, however, a shortage of transplantable human organs and this is unlikely to improve. Xenotransplantation – the transplantation of animal cells, tissues or organs into humans could therefore become an effective alternative to allotransplantation.

Current status

Attempts have already been made to transplant kidneys and livers into humans from chimpanzees and baboons; and hearts into humans from chimpanzees, baboons, pigs and sheep. To date however Xenotransplantation has been largely unsuccessful due to an inability to overcome immediate rapid onset rejection. To overcome rejection, use has been made of immunosuppressants and more recently, genetic modification of animals has been considered as a possible solution to the problem. Nonetheless, Xenotransplantation of organs has not yet reached the stage where it can be

successfully implemented but progress in science may make it a real possibility for the near future. Xenotransplantation of (immuno-isolated) cells seems to be the most likely area for initial clinical success.

The risks associated with Xenotransplantation are not only for the recipient, and could be widespread in terms of public health. The most immediate concern must be the possibility of infection of humans with Xenozoonoses – infections so far limited in their distribution to animal species. Xenotransplantation also raises major ethical concerns and has implications for animal husbandry.

Several member states of the European Community have given close consideration to the issue, but none has so far introduced regulatory requirements based on legislation. In response to the recommendations made in the report of the Advisory Group on the Ethics of Xenotransplantation "Animal Tissue into Humans" (Kennedy Report 1997), the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) was formed, but not on any statutory basis.

Where xenotransplants fall within the definition of a medicinal product under EC Pharmaceutical legislation they must be regulated at the clinical trials stage. A recent Commission Communication confirms that cell therapy, be it derived from human autologous/allogeneic or xenogeneic cells, must be considered as a medicinal product and regulated as such if the cells are processed so as to change their biological characteristics prior to administration.

A voluntary ban on the clinical application of Xenotransplantation has been adopted across Europe, but as scientific knowledge progresses, this voluntary ban is likely to be challenged.

The Council of Europe considered Xenotransplanation in 1997 and recommended a ban on its clinical application. These proposals were adopted voluntarily across Europe and a voluntary ban was placed on all clinical trials with xenotransplants, but this ban has not been underpinned by legislative or regulatory frameworks. It is understood that the Swedish Government is proposing to address these issues on a statutory basis, but no clinical trials using xenotransplants have to our knowledge been approved in any European member state.

Xenotransplantantion has already been used in clinical trials under close regulatory control in North America for the treatment of human disease in cohorts of carefully selected participants, but not yet as a routine therapy.

Assessment of the Risk

The potential risks posed by known or possible unknown infectious agents raises serious questions about the safety of xenotransplantation. This is an issue particularly for unprocessed material and whole organ transplants. Some infectious agents can cross species barriers as evidenced by transmission of porcine retroviruses in immunosuppressed mice. Whilst this does not necessarily mean that the viruses will cause harmful effects in the recipient species, it needs to be a matter for concern. The significance of these findings is still being considered. There are potential risks not only for the recipient but also more widespread in terms of public health and population effects, as well as implications for animal husbandry and major ethical concerns

Need for a Risk Assessment by the SSC

The definition and scope of the practice called “xenotransplantation” still needs to be carefully and sensibly worked out.

Already, several scientific and ethical bodies, national governments, and supranational interests have already made evaluations, and proposals. The Biotechnology Working Party of the EMEA is currently preparing a concept paper for xenogeneic cell therapy, but no pan-European policy has yet been established.

The FDA and the Canadian Health Protection Branch have already brought together preliminary views on the definition of xenotransplantation that may include products which come into contact with xenogeneic cells during processing, and each have proposed guidelines for regulatory control.

Already, leading scientific journals have signalled that now would be an appropriate time for Xenotransplantation to leave the laboratory and enter the clinic. If that is so, the public health and wider community issues might be better handled by a single approach across the European Community rather that individually by Member States as the public health implications are not limited by geographic boundaries. Now may therefore be an appropriate time to re-examine the scientific basis for concern and the options available safely to support or advance this practice of Xenotransplantation.

It is important to note the initial phase of the clinical development of xenotransplantation is unlikely to apply to whole organ transplant and that the current research on stem cell technology may compete with research in xenotransplantation for possibile treatments for conditions such as Parkinson’s disease, diabetes and skin replacement. Some experts believe stem cell technology offers a greater chance of success with a lesser concern over immunology and virological safety. It may therefore be important to assess the risks of the two emerging technologies together to compare them and project which may provide the safest option.

4. EFFECTS OF CONCERN

a) Endocrine disruption

There is growing concern on possible harmful consequences of exposure to xenobiotic compounds that are capable of modulating or disrupting the endocrine system. These so-called endocrine disrupting chemicals (EDCs) include persistent organochlorines, natural and synthetic steroid hormones, organotins, alkylphenols. Adverse effects on reproduction and development have been observed in a broad number of wildlife species representing many major taxa including mammals, birds, reptiles, fish and molluscs from Europe, North America and other continents. Most of these studies refer to aquatic food chain organisms. The observed abnormalities vary from subtle changes to overt and permanent structural and functional alterations, including disturbed sex differentiation with malformed (feminised or masculinised) sex organs, changed sexual behaviour, and altered immune function. Impaired reproduction and development causally linked to endocrine disrupting chemicals are well documented in a number of species and have caused local or regional population changes. For most of the reported effects in wildlife, however, the evidence for a causal link with endocrine disruption is limited. This is mainly due to the complexity of contaminant mixtures, the lack of data on both exposure and sensitivity of the

species concerned, along with a poor knowledge of the mechanisms of action. Crucial in establishing causal evidence for chemical-induced wildlife effects are semi-field or laboratory studies using the wildlife species of concern. Although most observed effects currently reported concern heavily polluted areas, there is a potential global problem. This is exemplified by the widespread occurrence of imposex in marine snails and the recent findings of high levels of persistent potential EDCs in several marine mammalian species inhabiting oceanic waters. Further studies are necessary to assess the environmental significance of endocrine disruption, which may eventually be harmful to humans.

b) Allergenicity

Summary of the Issue

Exposure to immunomodulating substances may among others lead to development of allergies. Dermal, respiratory and food allergenicity are known to occur and are believed to be caused by certain chemicals which may act as antigens by themselves or when bound to larger molecules. In addition, genetically modified foods are suspected to contain unknown proteins which may also sensitise man. Despite limited knowledge about mechanisms of development of allergy and its detection limited information is available concerning the existence of possible thresholds for sensitisation and challenge. Also recognition of possible structural alerts which are related to allergenic properties may be possible. Prediction of allergenicity, in subsets of the population in particular, and its relation to genetic predisposition seems urgently needed in order to better assess prospective developments.

Allergenic reactions should be discriminated from irritation, a well-known phenomenon, occurring in man, also in relation to food consumption.

Current status

Since allergic reactions to food components are a well established fact, there exists a real risk which may apply to a considerable part of the population. Development of novel foods, and the limited requirements for testing these, pose an additional risk.

Assessment of the risk

Allergic reaction may vary from light irritative effects to severe discomfort, including death, and may affect only a small sub-set of the population as well as a considerable number of persons in a population, depending on the substance and sensitivity of the recipient. Genetic predisposition may also be involved.

Need for a Risk Assessment by the SSC

The most immediate need is the development of appropriate, sufficient, sensitive, validated models to detect oral allergenicity. In its absence it may be recommended to develop instruments to detect possible allergic properties direct in man, for example by pre- or post-marketing surveillance of products likely to contain substances of sufficient molecular weight to act as allergens or substances which react with large molecules. Several authoritative reviews have been published concerning the phenomenon, but their exists a lack of a systematic methodological approach to detect oral allergenicity, as well as there is insufficient experience in

detecting allergens in pre- or post- marketing surveillance procedures. Considering the severity and possible extent of the risks this issue deserves high priority.

c) Climate change

Summary of the issue

Human economic activity has a strong impact on environment. Two of the best known global environmental changes are the accumulation of heat trapping greenhouse gases (GHG) in the lower atmosphere (troposphere) and the stratospheric ozone depletion. While for ozone depletion the health implications are relatively well known (skin cancer, cateract, immunosuppression) for temperature and weather changes as a result of global warming, one is much less informed. For example, extreme weather events may lead to exposures to thermal extremes with altered rates of heat/cold related illnesses or death, injuries or psychological disorders. Damage to public health infrastructure may be a result of altered frequencies and/or intensity of extreme weather events (e.g. due to floods or hurricanes). The likelihood that such extreme weather events will increase in number and intensity warrants us to consider the public health measures which can be developed to better control and/or curtail these in terms of changes in attitude or infrastructure.

Current status

Although some scientists still claim that the climatic change phenomenon has not been proved to occur, increasing support becomes available that extreme weather events do occur at higher frequencies than in the past causing thermal extremes as well as floods and hurricanes. The related risks are considerable and may consist of mortality due to the event, psychological disorders, increase in hitherto not occurring (vector-based) infectious diseases, starvation, regional economic disruption and the like.

Assessment of the risk

The severity of the risk may vary considerably and may range from slight discomfort to mortality. It will normally affect man locally or regionally and may affect even millions of people. Since climate changes may occur in the course of time, anticipation of the risk is a real option and successful prevention and/or remediation are an option.

Need for a risk assessment by the SSC

Insufficient information is currently available to fully understand the changes in space and time. In addition, only limited information is available on aspects such as dryness and its impact, or spread of (infectious) diseases to hitherto unaffected regions or countries.

Since effects on public health are also affected and complicated by socio-economic factors a multidisciplinary approach is needed to better understand and characterise the different risks for man involved in climate change. Intermediate to high priority.