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**United Nations  
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**Intergovernmental negotiating committee  
to prepare a global legally binding instrument  
on mercury**

**Third session**

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Item 3 of the provisional agenda\*

**Preparation of a global legally binding instrument  
on mercury**

**Addressing health in the mercury instrument**

**Note by the secretariat**

1. At its second session, held in Chiba, Japan, from 24 to 28 January 2011, the intergovernmental negotiating committee to prepare a global legally binding instrument on mercury requested the secretariat to provide information on health aspects of mercury issues and the use of mercury preservatives in medicine, including vaccines, for consideration by the committee at its third session.
2. In recognition of the expertise of the World Health Organization (WHO) and in view of the statements made by its representatives during the committee's first session and the organization's willingness to provide Governments with technical support relating to the management of health risks posed by mercury, the secretariat invited WHO to contribute to the preparation of the requested information. Annex I to the present note sets out a report by WHO on the use of mercury as a preservative in human vaccines, which has been reproduced as submitted, without formal editing. It presents information on the need for preservatives in vaccines, the quantities of mercury needed in the preparation of vaccines and health risks associated with the use of mercury in vaccines. It concludes that there is no evidence to suggest that the amount of thiomersal currently used in vaccines is sufficient to constitute a health hazard. The WHO also advises that thiomersal is used in human medicine as a preservative in other products including: plasma-derived products (anti-venoms, immunoglobulin preparations), clinical chemistry diagnostic kits for numerous infectious diseases, antibody preparations including skin test antigens, and immunoassay reagents. Thiomersal is also used in veterinary vaccines. Thiomersal is used in some pharmaceutical manufacturing processes.
3. In preparing the present note, the secretariat has also drawn on submissions from Governments provided in response to a request for information. The submissions have been summarized in annex II to the present note and may be viewed in full on the secretariat's website.<sup>1</sup>

**I. Background**

4. In section III of its decision 25/5, the Governing Council of the United Nations Environment Programme (UNEP) agreed that the committee, in developing a comprehensive and suitable approach

\* UNEP(DTIE)/Hg/INC.3/1.

<sup>1</sup> [www.unep.org/hazardoussubstances/Mercury/Negotiations/INC3/tabid/3469/Default.aspx](http://www.unep.org/hazardoussubstances/Mercury/Negotiations/INC3/tabid/3469/Default.aspx) and then click on "Submissions".

to mercury, should consider measures to address risks to human health and the environment as a consequence of anthropogenic mercury releases.

5. UNEP and WHO have previously prepared documents that provide information on the health effects of mercury. In addition, the secretariat has prepared several documents on the issue to support the committee's deliberations, including the following notes for the committee's second session:

- (a) Report on indicators to evaluate and track the health impacts of mercury and identify vulnerable populations (UNEP(DTIE)/Hg/INC.2/5);
- (b) Report on information on harmonized systems for measuring mercury body burden (UNEP(DTIE)/Hg/INC.2/6);
- (c) Executive summary of the document on guidance for identifying populations at risk from mercury exposure (UNEP(DTIE)/Hg/INC.2/19).

## II. Health effects of exposure to mercury<sup>2</sup>

6. All humans are exposed to some level of mercury; some are exposed to low levels, while others are exposed to higher levels, including acute exposures. The factors that determine the occurrence and severity of adverse health effects to exposure to mercury include the chemical form of the mercury concerned (including elemental mercury, inorganic mercury and organic mercury such as methylmercury and ethylmercury); the dose; the age or developmental stage of the person exposed (the foetus is considered to be the most susceptible); the duration of exposure; and the route of exposure (inhalation, ingestion or dermal contact). Dietary patterns such as fish consumption can increase exposure when fish and other seafood are contaminated with mercury.

7. The primary systems affected by mercury and mercury compounds are the nervous system, the kidneys and the cardiovascular system. It is generally accepted that developing organ systems (such as the foetal nervous system) are the most sensitive to toxic effects of mercury. Foetal brain mercury levels appear to be significantly higher than in maternal blood and the developing central nervous system of the foetus is currently regarded as the main system of concern because it demonstrates the greatest sensitivity. Other systems that may be affected include the respiratory, gastrointestinal, hematologic, immune and reproductive systems.

8. Effects on the nervous system (especially the developing nervous system) appear to be the most sensitive toxicological endpoint observed following exposure to elemental mercury and methylmercury, while damage to the kidneys is the key endpoint in exposure to inorganic mercury compounds. People are exposed to methylmercury primarily through their diet, especially through the consumption of fish and other marine species, as well as through the consumption of rice when it is grown in a methylmercury-rich environment. People may be exposed to elemental or inorganic mercury through inhalation of ambient air during occupational activities and from dental amalgams.

9. Thiomersal, which is used as a preservative in some vaccines and other medical products,<sup>3</sup> contains ethylmercury. The half-life of ethylmercury is six days compared with 40–50 days for methylmercury. Ethylmercury is actively excreted into the intestinal tract and not accumulated in the body. It rapidly converts to inorganic mercury, which is less toxic to the brain than ethylmercury or methylmercury. In the light of the nature of ethylmercury and the amounts found in thiomersal, WHO concludes in its report (set out in annex I) that "there is no evidence that suggest a possible health hazard with the amounts of thiomersal currently used, in particular no developmental nor neurological defects have been related to the use of this compound".

## III. Managing the risk of health impacts from mercury

10. The risks of impacts on health and the environment from mercury are a combination of the hazards associated with mercury, which are well known and thoroughly documented, and the extent of exposure to mercury.

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<sup>2</sup> Paragraphs 6–9 of the present document, summarizing the health effects of mercury, are drawn from the 2008 WHO/UNEP guidance document for identifying populations at risk from mercury exposure.

<sup>3</sup> Thiomersal is used in medicine as a preservative in products including human and animal vaccines, plasma-derived products (anti-venoms, immunoglobulin preparations), clinical chemistry diagnostic kits for numerous infectious diseases, antibody preparations, including skin test antigens, and immunoassay reagents. It is also used in some pharmaceutical manufacturing processes.

11. To reduce the risk of impacts on human health from mercury, it is essential to reduce exposure to mercury, for example by limiting the opportunities for direct exposure to mercury and by limiting exposure to mercury and its compounds from contaminated food or products containing mercury. The proposed instrument on mercury may establish a range of control measures to reduce the use of mercury and emissions and releases of mercury to the environment. Such control measures would seek to reduce the anthropogenic environmental load of mercury and thereby decrease human exposure through diet and other means. Depending on the control measures chosen, additional health benefits may be achieved, for example through the reduction of exposure to other pollutants hazardous to health.
12. It should be recognized that some level of mercury will always be present in the environment. Because mercury is an element, it cannot be destroyed or transformed into something else. Significant amounts of mercury are emitted or released as a consequence of natural events such as volcanic eruptions, forest fires and erosion. Accordingly, human exposure to mercury cannot be entirely eliminated. Nevertheless, eliminating or reducing anthropogenic emissions or releases of mercury could ensure that environmental levels are as low as possible. In particular, the mercury instrument will need to address meaningfully the major anthropogenic sources of mercury exposure so as to achieve public health objectives.
13. Measures to reduce the use of mercury in products, where efficient and effective alternatives exist, are intended to limit the direct exposure of humans to mercury from both occupational exposure during manufacturing, distribution and disposal of mercury-containing products and non-occupational exposure to products that are routinely available to the community, including when those products become waste. The use of mercury preservative-containing medicines, including vaccines, plasma-derived products and eye-drops, is already subject to regulation (by medical health regulators assessing safety, efficacy and quality of medical products before granting marketing authorization/registration).
14. Mercury is used in various processes in which there is potential for significant occupational exposure. Some processes are conducted in industrial plants, where there is an opportunity to manage worker health and safety under the guidance of relevant international agreements such as the Convention concerning Safety in the use of Chemicals at Work (Convention 170 of the International Labour Organization). Other processes using mercury, such as the amalgamation of gold in artisanal and small-scale gold mining, can, however, result in significant exposure to workers under conditions that are often uncontrolled and may lead to incidental exposure of others.
15. Providing information to raise awareness of the risks of mercury, and on ways to minimize or eliminate exposure to mercury, may also reduce the public health impact of mercury.
16. One means of assessing the success of the proposed mercury instrument in reducing exposure to mercury could be to institute monitoring and evaluation programmes, including biomonitoring of mercury levels in the environment, which could provide a mechanism for tracking progress in reducing overall mercury exposure.
17. The reports on indicators to evaluate and track the health impacts of mercury and identify vulnerable populations (UNEP (DTIE)/Hg/INC.2/5) and on information on harmonized systems for measuring mercury body burden (UNEP(DTIE)/Hg/INC.2/6), both prepared by WHO, deal with this issue. In the case of human exposure to methylmercury, human biomonitoring through hair analysis is recommended, and is preferred to monitoring of mercury levels in fish because the latter provides an indirect indicator of human exposure with greater inherent uncertainty than hair analysis. Analysis of urine samples is considered to be the best means of determining the body burden of mercury from long-term exposure to elemental and inorganic mercury.

#### **IV. Coverage of health aspects in other multilateral environmental agreements and conventions**

18. None of the Basel Convention on Transboundary Movement of Hazardous Wastes and Their Disposal, the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade or the Stockholm Convention on Persistent Organic Pollutants include articles specifically dedicated to health aspects. Instead, the protection of human health (and the environment) is the underlying goal of each instrument. Both the Rotterdam and Stockholm conventions explicitly state that their objective is to protect human health and the environment. The Basel Convention does not include an article on the Convention's objective; its preamble, however, states that the parties are determined to protect, by strict control, human health and the environment.

19. Likewise, the WHO Framework Convention on Tobacco Control states in its objective that the Convention aims “to protect present and future generations from the devastating health, social, environmental and economic consequences of tobacco consumption and exposure to tobacco smoke...”.

20. Other than in their objectives or preambles, the instruments include few provisions on human health, and instead feature control measures to reduce the supply of, demand for and release of the substances that they target with the aim of reducing exposure and thus the risk of impacts on human health (and the environment).

21. In recognition of the importance of the Basel and Stockholm conventions as a means of improving human health, the World Health Assembly has adopted resolution WHA50.13 on promotion of chemical safety, with special attention to persistent organic pollutants. It has also adopted resolution WHA63.25, on improvement of health through safe and environmentally sound waste management, and resolution WHA63.26 on improvement of health through sound management of obsolete pesticides and other obsolete chemicals. In those resolutions, the Assembly has endorsed action to protect human health and the environment through sound chemicals management and expressed support for the continuing activities under the Basel and Stockholm conventions.

22. The World Health Assembly has also recognized the importance of sound management of chemicals in its resolution WHA59.15, on the Strategic Approach to International Chemicals Management, a principal objective of which is to minimize risks posed by chemicals throughout their lifecycle to human health, including that of workers, and to the environment. By this resolution the Assembly has welcomed the Strategic Approach and urged its member States to take full account of the health aspects of chemical safety in national implementation of the Strategic Approach; to participate in national, regional and international efforts to implement the Strategic Approach; and to nominate national Strategic Approach focal points from the health sector. It has also requested the Director-General of WHO to facilitate implementation of the Strategic Approach by the health sector and to provide support for implementation by working with partners in the International Labour Organization and the Inter-Organization Programme for the Sound Management of Chemicals.

## **V. Possible considerations for the committee**

23. The committee may wish to consider how comprehensive the provisions of the future mercury instrument should be to obtain the desired reductions in environmental emissions and releases of mercury and protection of human health. In addition, the committee may wish to consider the need for any additional provisions that might be necessary to provide further protection to particularly vulnerable populations. The committee may also wish to guard against any unintended effects of the provisions of the treaty, such as limiting access to medical products, which may, unintentionally, adversely affect the public health. Parties who are members of the World Health Assembly may wish to consider in that forum, either during the negotiation of the mercury instrument or following its entry into force, the role of the public health sector in facilitating and supporting the implementation of the instrument to address the negative public health impact of mercury exposure.

## Annex I

### Mercury in human vaccine preservatives (submitted by WHO)

#### *Background*

1. Thiomersal (also known as thimerosal, mercurothiolate and sodium 2-ethylmercuriothio-benzoate) is an ethyl mercury-containing antimicrobial compound used to prevent bacterial and fungal growth in some vaccines during storage, and especially during use of opened multi-dose vials. It is also used during vaccine production both to inactivate certain organisms and toxins and to maintain a sterile production line. Thiomersal has been used since the 1930s in the manufacture of some vaccines and other medicinal products.

#### *Why do vaccines need preservatives?*

2. In many countries, for multi-dose vaccines, other than live vaccines, the presence of a preservative is a regulatory requirement. Preservatives inhibit growth of bacterial and fungal contamination, which may be introduced during repeated puncture of a multi-dose vial septum. While a preservative is needed only for multi-dose presentations, a manufacturer will usually make one bulk formulation, so if the product has both multi-dose and single dose presentations, the single dose presentation would also contain preservative.

3. Opened vials of vaccines without preservatives need to be discarded at six hours from opening or at the end of the immunization session, whichever is earlier. The presence of a suitable preservative means that opened multi-dose vials may be kept for use in subsequent immunization sessions (WHO policy statement, 2000). This minimizes wastage and can have a significant impact on programme costs. Based on known patterns of vaccine administration in different countries WHO estimates that at least 30% of vaccine doses required can be saved through application of this policy to preserved multi-dose vials.

#### *Very small amounts of mercury are used for vaccine preservative*

4. Vaccines that contain thiomersal include those against diphtheria, tetanus and pertussis (DTP), hepatitis B, Haemophilus influenzae type b (Hib), rabies, influenza and meningococcal diseases. Usually, these have thiomersal added in varying concentrations (8 to 50 µg per dose) as a preservative. This list is not exhaustive, but highlights vaccines of major global public health importance. Also, some vaccines may contain trace amounts of thiomersal (<0.5 µg per dose), if it has been used in the production process as an inactivating agent, but has not been added to the final product as a preservative.

5. Currently thiomersal-containing vaccines are supplied by the United Nations (UNICEF and WHO Regional Office for the Americas in particular) with multi-dose presentations of thiomersal containing vaccines. These vaccines form the basis of the prevention of at least four major killers of infants and children (diphtheria, tetanus, pertussis, Haemophilus influenzae type b disease and influenza) and one other important disease (hepatitis B). During 2010, UNICEF alone supplied over 300 million doses of vaccines against those diseases either for routine vaccination activities or for response against outbreaks of infectious diseases such as influenza or epidemic meningitis.

6. Data from the European Union, where two large manufacturers of inactivated vaccines are located, reveal that the total quantity of thiomersal utilized by members of European Vaccine Manufacturers (EVM) is less than 0.25 ton per year corresponding to 0.125 ton of mercury. A significant part of this is used for vaccines exported to developing countries. In summary, the quantities of mercury involved with vaccine preservatives are fairly small.

#### *Safety of thiomersal*

7. Health risks related to the use of thiomersal in vaccines have been reviewed on numerous occasions. In 1999, concerns were raised in the United States of America regarding exposure to mercury following immunization with thiomersal-containing vaccines. This was based on the calculation that the cumulative amount of mercury in infant immunization schedules potentially exceeds the recommended threshold for methyl mercury set by a USA government agency. However, thiomersal contains ethyl mercury, not methyl mercury. The pharmacokinetics of ethyl and methyl mercury are quite different. In particular, the half-life of ethyl mercury is short (6 days; 95% CI: 3-10 days) compared with 40-50 days for methyl mercury. Ethyl mercury is actively excreted into the intestinal tract and not accumulated in the body.

8. Since August 2000, the WHO Global Advisory Committee on Vaccine Safety (GACVS) has periodically reviewed available information on thiomersal pharmacokinetic studies in humans (including low birthweight infants) and in monkeys and has assessed the validity of animal models in studying associations between thiomersal and neurobehavioural disorders in humans:

- Expert consultation and data presented to the GACVS indicate that the pharmacokinetic profile of ethyl mercury is substantially different from that of methyl mercury. The half-life of ethyl mercury is shorter compared to methyl mercury (see above) making exposure to ethyl mercury in blood comparatively brief and preventing accumulation when vaccines are administered at least four weeks apart. Further, ethyl mercury is actively excreted via the gut unlike methyl mercury that accumulates in the body. This rapid elimination of ethyl mercury has been confirmed in all studies reviewed, even those that looked at low birthweight infants.
- Four independent epidemiological studies investigating associations and frequency of neurobehavioural disorders in relation to vaccination with thiomersal-containing vaccines from the United Kingdom and Denmark did not challenge the safety of existing thiomersal-containing vaccines in infants. In particular analyses in the U.K. of the General Practice Research Database (GPRD) and of the data set of the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) suggest that there is no association between developmental delay, adverse neurological developmental outcomes or behavioural problems, and thiomersal-containing diphtheria–pertussis–tetanus vaccines.
- GACVS also reviewed a series of studies by Geier and Geier alleging reduction of neurodevelopmental disorders in the United States of America following discontinuation of thiomersal-containing vaccines in the national immunization programme. The Committee found a number of limitations, including: inaccessibility to the reader of the data on which the analysis was made; lack of clear case definitions for the conditions referred to in the paper; unclear or insufficient description of applied statistical methods; assumption made by the authors that the toxicity of ethyl-mercury is equivalent to that of methyl-mercury (an assumption that cannot necessarily be made, and against which various authorities have warned); assumption in the paper that the populations under study are similar (there is every possibility in the methods used of selection bias); and a failure to account for changing reporting patterns for diseases attributed to the vaccines over the years of the study. Published outcomes regarding neurodevelopment and heart disease following administration of thiomersal-containing vaccines do not meet the scientific criteria required to suggest causal relationship. The Committee therefore found the conclusions made by these authors unconvincing.

9. On that basis the GACVS considers that pharmacokinetic and developmental studies do not support concerns over the safety of thiomersal in vaccines. The Committee concludes, and advises accordingly, that there is no reason on grounds of safety to change current immunization practices with thiomersal-containing vaccines, as the risks are unproven.

10. Similar conclusions were reached by other respected advisory committees such as those from:

- U.S. Institute of Medicine (2001). *"The hypothesis that thimerosal exposure through the recommended childhood immunization schedule has caused neurodevelopmental disorders is not supported by clinical or experimental evidence."*
- American Academy of Pediatrics (2003). *"No scientific data link thimerosal used as a preservative in vaccines with any pediatric neurologic disorder, including autism."*
- UK Committee on Safety of Medicines (2003). *"There is no evidence of harm caused by doses of thiomersal in vaccines, except for hypersensitivity reactions (such as allergic skin reactions). There is no evidence of a link between hypersensitivity reactions and the development of autism."*
- European Agency for the Evaluation of Medicinal Products (2004). *"Recent Evidence Supports Safety of Thiomersal Containing Vaccines."*

**Public health implications of restricting manufacture, distribution or use of thiomersal-containing vaccines**

11. Thiomersal-containing vaccines are the most commonly used form of vaccine presentation to protect more than 80 million infants from deadly diseases every year. Making vaccines thiomersal free

would require either using alternative preservatives (2-phenoxyethanol, phenol and benzethonium chloride are preservatives used in a small number of other licensed vaccines) or using preservative-free single dose vaccines exclusively.

12. However, either of the above changes to products currently formulated with thiomersal would require regulatory approval (WHO - Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines, 2004). There is no guarantee of obtaining a vaccine of equivalent quality, safety and efficacy following replacement of thiomersal as an inactivating agent or replacement or removal of thiomersal as the preservative from an existing licensed product. This could require a new licensing application, including conducting of new manufacturing validation studies; pre-clinical and clinical studies. This is time consuming and costly, could lead to an increase in vaccine cost and could interrupt global supply of the vaccines.

13. Vaccines could be supplied in preservative-free single-dose vials as is the case for the majority of vaccines used in industrialized countries. This option, however, requires a significant increase in manufacturers' filling capacity. This would be time consuming and expensive to implement and it may not be possible to produce sufficient single dose product to ensure uninterrupted global supply. Vaccines supplied in single dose vials are more expensive than a dose of vaccine from a multi-dose vial. In addition, single-dose vials require significantly larger cold storage space as well as increased transport capacity, which is currently not feasible for the majority of countries. Current WHO estimates suggest that the vaccine storage requirements would at least double if single dose presentations only were used (WHO vaccine volume calculator, March 2011). Upgrading the cold chains of those countries is limited by local resources and the additional maintenance requirements that would render many existing systems vulnerable.

#### ***WHO position on the use of thiomersal in vaccines***

14. The assessment of thiomersal as a preservative for vaccines suggests that the amount of mercury involved with thiomersal use in vaccines is small compared to other sources of mercury.

15. WHO has closely monitored scientific evidence related to the use of thiomersal as a preservative for multi-dose inactivated vaccine presentations for over ten years, in particular through its independent expert advisory group GACVS. Although many alleged risks have been studied in detail in different groups of infants, there is no evidence that suggest a possible health hazard with the amounts of thiomersal currently used, in particular no developmental nor neurological defects have been related to the use of this compound.

16. WHO recommends multi-dose vaccine vials for the routine immunization programs in many countries because they are safe and effective, they limit the required storage capacity and help reduce vaccine costs. There is no likelihood of timely supply of sufficient alternative thiomersal-free presentations of inactivated vaccines. Alternative presentations would incur significantly higher costs in manufacturing procedures and regulatory approval, thereby limiting the ability to offer affordable vaccines against major killer diseases where those products are the most needed.

UNEP DTIE Chemicals Branch and WHO Department of Food Safety, Zoonoses and Foodborne Diseases 2008. Guidance for identifying populations at risk from mercury exposure.

<http://www.who.int/entity/foodsafety/publications/chem/mercuryexposure.pdf>

European Commission Directorate-General Environment 2008. Options for reducing mercury use in products and applications, and the fate of mercury already circulating in society. Final report. [http://ec.europa.eu/environment/chemicals/mercury/pdf/study\\_report2008.pdf](http://ec.europa.eu/environment/chemicals/mercury/pdf/study_report2008.pdf)

WHO 2000. WHO Policy Statement - The use of opened multi-dose vials of vaccine in subsequent immunization sessions.

<http://www.who.int/vaccines-documents/DocsPDF99/www9924.pdf>

WHO Global Advisory Committee on Vaccine Safety (2006). Statement on thiomersal  
The Global Advisory Committee on Vaccine Safety concludes that there is no evidence of toxicity in infants, children or adults exposed to thiomersal (containing ethyl mercury) in vaccines.

[http://www.who.int/vaccine\\_safety/topics/thiomersal/statement\\_jul2006/en/index.html](http://www.who.int/vaccine_safety/topics/thiomersal/statement_jul2006/en/index.html)

WHO Global Advisory Committee on Vaccine Safety (2006). Thiomersal and vaccines: questions and answers.

[http://www.who.int/vaccine\\_safety/topics/thiomersal/questions/en/index.html](http://www.who.int/vaccine_safety/topics/thiomersal/questions/en/index.html)

WHO Global Advisory Committee on Vaccine Safety. Meeting reports from December 2004, June 2005 and June 2008.

<http://www.who.int/wer/2008/wer8332.pdf>

<http://www.who.int/wer/2005/wer8028.pdf>

<http://www.who.int/wer/2005/wer8001.pdf>

WHO Expert Committee on Biological Standardization (2004). Fifty-third Report. Annex 4  
Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines. PP 95-102.

[http://whqlibdoc.who.int/trs/WHO\\_TRS\\_926.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_926.pdf)

Knezevic I, Griffith E, Reigel F, Dobbelaer R (2003). Thiomersal in vaccines: a regulatory perspective (meeting report).

[http://www.who.int/biologicals/publications/meetings/areas/vaccines/thiomersal/Thiomersal\\_WHO\\_Consult%20April%2015\\_16\\_April2002.pdf](http://www.who.int/biologicals/publications/meetings/areas/vaccines/thiomersal/Thiomersal_WHO_Consult%20April%2015_16_April2002.pdf)

WHO. Vaccine volume calculator.

[http://www.who.int/immunization\\_delivery/systems\\_policy/logistics/en/index4.html](http://www.who.int/immunization_delivery/systems_policy/logistics/en/index4.html)

WHO. Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines, 2004). WHO Technical Report Series, No. 926, 2004.

[http://www.who.int/biologicals/publications/trs/areas/vaccines/thiomersal/Annex%20\(95-102\)TRS926thiomersal.pdf](http://www.who.int/biologicals/publications/trs/areas/vaccines/thiomersal/Annex%20(95-102)TRS926thiomersal.pdf)

## Annex II

### Summaries of information submitted by Governments on the use of mercury preservatives in medicine, including vaccines

1. Summaries of the information submitted by Governments on the use of mercury preservatives in medicine, with a focus on current use, are provided below.

#### Canada

2. The Government of Canada indicates that vaccines approved for use in Canada are classified in three broad categories:

- (a) No thiomersal: where no thiomersal has been used in any part of the manufacturing process;
- (b) Trace amounts of thiomersal (less than 1.0 micrograms per dose): where thiomersal is used during production, but is not added to the final product as a preservative;
- (c) Thiomersal added as a preservative: typically those supplied in multi-dose vials, where thiomersal is added to prevent contamination with other serious infectious agents. The amount of mercury per 0.5 ml dose varies from 2 to 50 micrograms.

3. Preservatives play an important role in vaccine safety, particularly in multi-dose vials, while single-dose vials do not generally need preservatives. Single-dose vials, however, are significantly more expensive and may not be convenient to use in large-scale immunization programmes such as for influenza. Research on alternatives to thiomersal is continuing, and it is important that such research be supported, particularly as current alternatives such as phenoxyethanol are available but are generally less effective than thiomersal.

4. In Canada some multi-dose preparations of influenza or hepatitis B vaccines are the only thiomersal-containing products that might be offered to children as part of the routine childhood immunization schedule. Thiomersal-free influenza and hepatitis B vaccines have also become available in recent years.

5. The Canadian National Advisory Committee on Immunization reaffirms its recommendations:

- (a) There is no legitimate safety reason to avoid the use of thiomersal-containing products for children or older individuals, including pregnant women. Some contraindications, in particular reactions to previous immunizations, may preclude the use of thiomersal-containing products;
- (b) The long-term goal of removing thiomersal from vaccines, provided that there are safe alternatives to ensure that multi-dose vials are sterile, continues to apply, since this is one achievable way to reduce total environmental exposure to mercury.

#### Croatia

6. The Government of Croatia advises that the Croatian Agency for Medicines and Medicinal Products has approved thiomersal as a preservative in some medicines and vaccines. The submission provides details with regard to the specific types of vaccines and concentrations that have been approved.

#### Japan

7. The Government of Japan advises that thiomersal is used, and has advantages, as a preservative for vaccines. Pharmaceutical companies have been making efforts to reduce the amount of thiomersal used and to increase the use of alternatives and single-dose containers. The use of thiomersal will continue to be necessary in some situations, such as pandemics.

8. The amount of thiomersal and mercury used in vaccines manufactured in Japan in 2009 was approximately 127 grams (equivalent to some 63 grams of mercury). The submission also provides details with regard to the specific types of vaccines and concentrations that have been approved.

#### Norway

9. The Government of Norway advises that, while a general ban on the manufacture, import, export, sale and use of substances or preparations containing mercury or mercury compounds in concentrations above 0.001 per cent by weight was introduced in 2008, the use of thiomersal in vaccines is permitted. This exemption is based on the notion that in certain situations the use of

multi-dose vaccine containers is warranted. Thiomersal is added to multi-dose containers to prevent fungal and bacterial contamination. It is not added to vaccines in single-dose containers and mercury-containing preservatives have not been used in vaccines for the childhood immunization programme since 1997. Influenza vaccines for the annual flu on the Norwegian market do not contain thiomersal. Manufacturers have been encouraged to develop vaccines that are free of thiomersal, and all other uses of mercury as a medical preservative are banned in Norway.

10. The multi-dose influenza vaccine for the new influenza A (H1N1) strain, Pandemrix, was used for a mass vaccination in the pandemic situation in 2009–2010, with 2.2 million people vaccinated. The total amount of mercury used was 5.5 grams. In a small number of vaccines thiomersal is added at an early stage in the production process but is significantly reduced in processing. The mercury concentration is considerably lower when used as a preservative, falling below the general ban limit value of 0.001 per cent mercury by weight.

11. For veterinary use multi-dose vaccines containing thiomersal are routinely employed, especially for herd animals. Based on the number of doses sold by wholesalers, the total quantity of mercury used in all vaccines for veterinary uses in 2010 was approximately 40 grams.

12. Mercury was previously used as a medical preservative in Norway in two eye-drop products, but this use was phased out in 2003 when thiomersal was replaced with benzalconchloride.

### **Tajikistan**

13. The Government of Tajikistan reports that the country's medical facilities currently use the medical preservative Merthiolate, which is an organic salt of mercury, to ensure the stability of vaccines.

### **United States of America**

14. The Government of the United States has submitted information on the safety and current status of thiomersal, which is used in some vaccines licensed by the United States Food and Drug Administration (FDA).

15. With the exception of influenza vaccines, all vaccines manufactured since 2001 that are routinely recommended in the United States for children six years of age and under are presented in single-dose formulations and do not contain thiomersal as a preservative. Some may contain trace amounts of thiomersal used as part of the manufacturing process. As with paediatric vaccines, exposure to thiomersal in vaccines for adolescents and adults has also been reduced or eliminated. The use of thiomersal as a preservative in licensed vaccines has thus fallen greatly over the past decade.

16. The exception is inactivated influenza virus vaccines, which continue to be marketed in both thiomersal-free single-dose and thiomersal-containing multi-dose formulations. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices does not preferentially recommend thiomersal-free vaccines for any populations. Notably, of the 160 million doses of FDA-licensed seasonal influenza vaccine distributed during the 2010–2011 season, approximately 90 million were in multi-dose vials containing thiomersal. The United States considers that the availability of influenza vaccines formulated in multi-dose vials is critical in situations of influenza pandemic. Moreover, it believes that vaccines formulated in multi-dose vials containing thiomersal as a preservative remain an important component of immunization programmes in developing countries because of their reduced cost and storage requirements.

17. FDA has not identified any preservative as effective as thiomersal. Some have suggested the use of 2-phenoxyethanol as an alternative; this substance has not, however, been widely used as a preservative in vaccines licensed in the United States and for some vaccines has not been shown not to be effective as a preservative when used alone.

18. The United States also provides information on notable studies and assessments of the use of thiomersal in vaccines, studies evaluating the kinetics and toxicity of ethylmercury compared to methylmercury and studies on the association between thiomersal and autism. Information is also provided on recent United States court decisions.

19. The United States concludes that licensed vaccines containing thiomersal as a preservative have been determined to be safe and effective under applicable statutory and regulatory requirements and therefore are approved for use in the United States.