World Health Organization

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Reports of advisory bodies

Expert committees and study groups[1]

Report by the Secretariat

EXPERT COMMITTEE ON DRUG DEPENDENCE

Thirty-sixth meeting of the Expert Committee on Drug Dependence[2] Geneva, 16–20 June 2014

1. The Expert Committee on Drug Dependence was composed of 14 experts from the six WHO regions. Meeting participants also included advisers to the Secretariat as well as observers from the United Nations Office on Drugs and Crime (UNODC), and the International Narcotics Control Board. Twenty-six substances were assessed and recommendations for placing psychoactive substances under international control have been conveyed to the Commission on Narcotic Drugs, which will make the final decision on scheduling in March 2015.

Main recommendations

2. The Expert Committee recommended that the substances listed below be placed under international control:

(a) in Schedule I of the 1961 Convention: AH-7921, chemical name 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide

(b) in Schedule I of the 1971 Convention:

- gamma-butyrolactone (GBL), chemical name oxolan-2-one
- 1,4-butanediol (butane-1,4-diol, 1,4-BDO or 1,4-BD)

[1] The Regulations for Expert Advisory Panels and Committees provide that the Director-General shall submit to the Executive Board a report on meetings of expert committees containing observations on the implications of the expert committee reports and recommendations on the follow-up action to be taken.

[2] WHO Technical Report Series, No. 990 (in press).

- 25B-NBOMe (2C-B-NBOMe), chemical name 2-(4-bromo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine

- 25C-NBOMe (2C-C-NBOMe), chemical name 2-(4-chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine

- 25I-NBOMe (2C-I-NBOMe), chemical name 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine

(c) in Schedule II of the 1971 Convention:

- *N*-benzylpiperazine (BZP), chemical name 1-benzyl-1,4-diazacyclohexane

- JWH-018, chemical name naphthalen-1-yl-(1-pentyl-1*H*-indol-3-yl)methanone

- AM-2201, chemical name [1-(5-fluoropentyl)-1*H*-indol-3-yl](-naphthalen-1-yl)methanone

- 3,4-methylenedioxypyrovalerone (MDPV), chemical name (*R,S*)-1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one

- methylone (beta-keto-MDMA), chemical name (*R,S*)-1-(1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one

- mephedrone, chemical name (*R,S*)-2-methylamino-1-(4-methylphenyl)propan-1-one.

3. With regard to mephedrone, a notification to the United Nations Secretary-General had been made by the United Kingdom of Great Britain and Northern Ireland, pursuant to article 2, paragraphs 1 and 3 of the Convention on Psychotropic Substances, 1971, concerning a proposed recommendation for international control of mephedrone. Preliminary data collected from the literature and from countries indicate that mephedrone may cause substantial harm.

4. The Expert Committee critically reviewed this substance and considered that the degree of risk to public health and society associated with the abuse liability of mephedrone is substantial. There are no data on therapeutic usefulness. The Committee therefore considered that the placement of mephedrone under international control was warranted, given the evidence of its abuse.

5. **The Expert Committee recommended that the following substances are not placed under international control:**

- tapentadol hydrochloride (International Non-proprietary Name), chemical name 3-[(1*R*,2*R*)-3-dimethylamino-1-ethyl-2-methylpropyl]phenol hydrochloride

- JWH-073, chemical name (1-butyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanone

- UR-144, chemical name (1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone

- APINACA (AKB-48), chemical name *N*-(adamantan-1-yl)-1-pentyl-1*H*-indazole-3-carboxamide
- RCS-4, chemical name 4-methoxyphenyl-(1-pentyl-1*H*-indol-3-yl)methanone
- JWH-250, chemical name 2-(2-methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone
- 4-methylethcathinone (4-MEC), chemical name (*R*,*S*)-2-ethylamino-1-(4-methylphenyl)propan-1-one
- 4-fluoromethcathinone (flephedrone; 4-FMC), chemical name (*R*,*S*)-1-(4-fluorophenyl)-2-methylaminopropan-1-one
- alpha-methyltryptamine (AMT) chemical name 2-(1*H*-indol-3-yl)-1-methylethylamine with (*R*) and (*S*) stereoisomers
- methoxetamine, chemical name 2-(3-methoxyphenyl)-2-ethylaminocyclohexanone
- methiopropamine (MPA), chemical name 1-(thiophen-2-yl)-2-(methylamino)propane
- ketamine (International Non-proprietary Name), chemical name (±)-2-(2-chlorophenyl)-2-methylaminocyclohexanone.

6. With regard to ketamine, a notification to the United Nations Secretary-General had been made by China, under the Convention on Psychotropic Substances, 1971,[1] concerning a proposed recommendation for international control of ketamine. The Expert Committee critically reviewed this substance. It acknowledged the important medical use of ketamine as an anaesthetic, especially in low- and middle-income countries, in crisis situations and for veterinary use, because of its safety margin and its ease of use. The Committee took note of concerns raised by some countries and organizations within the United Nations system with respect to the potential for ketamine abuse. The Committee considered that the risk to public health posed currently by ketamine abuse on a global scale does not warrant its scheduling. Consequently, the Committee recommended that ketamine not be placed under international control at this time. The Committee recognized, however, that in countries where such abuse is a problem, putting ketamine under national control may be considered.

7. **For psychoactive substances for which pre-reviews[2] were carried out, the thirty-sixth Expert Committee recommended that critical reviews[3] were not warranted for:**

- lisdexamfetamine (International Nonproprietary Name), chemical name (2*S*)-2,6-diamino-*N*-[(2*S*)-1-phenylpropan-2-yl]hexanamide,(2*S*)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate

[1] Convention on Psychotropic Substances, 1971, Article 2, paragraph 1; see https://www.unodc.org/pdf/convention_1971_en.pdf (accessed on 25 November 2014).

[2] **Pre-review:** An initial review to determine whether a critical review is warranted ("the purpose of the pre-review is to determine whether current information justifies an Expert Committee critical review").

[3] **Critical review:** a review to make decisions on scheduling or a change in scheduling ("is to consider whether the Expert Committee should advise the Director-General to recommend the scheduling of, or amending of the scheduling status of, a substance").

- tramadol (International Nonproprietary Name), chemical name (±)-*trans*-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol.

Other matters

8. WHO and UNODC proposed that an international consultation take place in December 2014, the aim of which is to review criteria for the selection of new psychoactive substances to be assessed by the thirty-seventh meeting of the Expert Committee. It is expected that this consultation would also explore how to improve and align indicators, methodologies and tools for data collection on abuse, dependence potential and public health risks of new psychoactive substances, by the various international and regional agencies. The outcomes of the consultation are expected to contribute to broader goals, which include the generation of robust data, the minimization of duplicated effort, and the facilitation of data collection in countries. The Secretariat will also use pharmacovigilance data on abuse and dependence potential for the review and assessment of substances using the Uppsala Monitoring Centre VigiBase database.

Significance for public health policies

9. The substances that have been recommended for scheduling by the Expert Committee at its thirty-sixth meeting are considered to present risks in terms of abuse, dependence and public health. Substances that present substantial public health risks have been placed in Schedule II of the Convention on Psychotropic Substances, 1971. Those that present especially serious public health risks have been placed in Schedule I of that Convention.

10. Substances with a medical use, such as tapentadol hydrochoryde (International Nonproprietary Name Modified) and ketamine (International Nonproprietary Name), were critically reviewed. For both substances, the Committee recommended not to place them under international control.

11. Tapentadol is primarily prescribed and dispensed on an outpatient basis for those with osteoarthritis, joint pain or chronic pain, and for whom other medications have not been effective. Currently, the data available are not sufficient to carry out a sound assessment of the potential for dependence or abuse, or with respect to the public health risks of this medication.

12. Ketamine is widely used as an anaesthetic in human and veterinary medicine, especially in low- and middle-income countries and crisis or emergency situations. The ease of parenteral administration gives ketamine a major advantage when anaesthetic gases are impossible to use due to limited equipment and lack of appropriately trained specialists. In many countries, there are no suitable alternatives that are affordable. Ketamine has, in addition, a wide margin of safety when compared with other anaesthetic agents.

Implications for the Organization’s programmes

13. A Note Verbale to the United Nations Secretary-General has conveyed the recommendations of the Expert Committee on scheduling of psychoactive substances for further decision by the Commission on Narcotic Drugs.

14. Owing to the high number of new psychoactive substances recently identified, work continues on defining relevant criteria for the selection and prioritization of new psychoactive substances for assessment by the Expert Committee. This will ensure that the Committee reviews priority substances for which sufficient robust data are available. WHO indicators, methodologies and tools for collection

of data on new psychoactive substances in countries, such as availability, use, abuse, dependence and public health risks, will be improved and aligned with other international and regional organizations, including UNODC and the European Monitoring Centre for Drugs and Drug Addiction.

15. Preparations are in place for the thirty-seventh meeting of the Expert Committee. Reviews will be commissioned and peer reviews carried out. A global country survey to include 194 WHO Member States and focusing on psychoactive substances will be conducted to assess substance availability, use, abuse, dependence and public health risk, among others. These data and those from other sources, including from the Uppsala Monitoring Centre, UNODC and the European Monitoring Centre for Drugs and Drug Addiction, will be analysed and will inform the reviews carried out by the thirty-seventh meeting of the Expert Committee.

16. The Secretariat is also active in advocating for and supporting the implementation of balanced country-level policies, that is, policies that aim for a balance between improving the availability of controlled medicines, and preventing their misuse, diversion and trafficking, in line with the United Nations international drug control conventions.[1]

17. In May 2014, the Sixty-seventh World Health Assembly adopted resolution WHA67.19 on the strengthening of palliative care as a component of comprehensive care throughout the life course, thereby providing strong support for the work of the Organization, at global and country levels, on improving access to and use of medicines for palliative care. WHO is part of ATOME, a consortium that has a presence in 12 European countries and is funded by the European Commission, and that works to improve access to opioid medications in Europe. In addition, a joint global programme is being undertaken by WHO, the Union for International Cancer Control and UNODC on access to controlled drugs for medical purposes, the objective of which is to improve access to controlled medicines, particularly pain medication.

EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Seventy-eighth Joint FAO/WHO Expert Committee on Food Additives Geneva, 5–14 November 2013[2]

Main recommendations

18. The Committee performed risk assessments and made recommendations on the safety of residues of eight veterinary drugs when used for food-producing animals and used in accordance with good veterinary practices. Acceptable daily intake values for these drugs were established and maximum residue limits that are compatible with human health were recommended for specified animal species and tissues.

19. The report presents general considerations and guidance, in particular on improved risk assessment methodologies, on the extrapolation of maximum residue limits to minor animal species and commodities, and on the establishment of maximum residue limits for honey.

[1] For more information on WHO guidance, see *Ensuring balance in national policies on controlled substances*, at: http://www.who.int/medicines/areas/quality_safety/guide_nocp_sanend/en/index.html (accessed on 28 November 2014).

[2] Evaluation of certain veterinary drug residues in food (Seventy-eighth report of the Joint FAO/WHO Expert Committee on Food Additives) WHO Technical Report Series, No. 988, 214 (in press).

20. The Committee also discussed work undertaken by WHO in relation to antimicrobial resistance as it relates to the work of the Joint Expert Committee, and decided to follow closely further developments and to apply those aspects relevant to its work.

21. The assessments, recommendations and comments provided by the Committee will be discussed by the Codex Committee on Residues of Veterinary Drugs in Food, and will result in the identification of appropriate risk management and risk-mitigation measures to reduce human exposure where necessary, and in recommendations to national authorities for the safe use of these veterinary drugs in food-producing animals.

22. WHO has published detailed monographs of toxicological and other related information upon which the safety assessments of the compounds were made;[1] FAO has published detailed residue monographs.[2]

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Seventy-ninth Joint FAO/WHO Expert Committee on Food Additives Geneva, 17–26 June 2014[3]

Main recommendations

23. The Committee evaluated the safety of nine food additives, revised the specifications for five other food additives and evaluated 28 flavouring agents according to the Procedure for Safety Evaluation of Flavouring Agents.

24. The report presents general considerations and guidance, in particular on improvements in the safety assessment methodology for the evaluation of flavouring agents, and for limiting contamination in food additives for use in infant foods.

25. These assessments, recommendations and comments provided by the Committee will be discussed by the Codex Committee on Food Additives, to provide recommendations to national authorities for the safe use of these food additives and to identify and recommend appropriate risk management and risk-mitigation measures to reduce human exposure, where necessary.

26. WHO will publish detailed monographs of the toxicological and other related information upon which the safety assessments of the compounds were based in the WHO Food Additives Series.[4] FAO publishes summaries of the identity and purity of food additives.

[1] Toxicological evaluation of certain veterinary drug residues in food. WHO Food Additives Series No. 69, 2014. For further information on the WHO Food Additives Series, see: http://www.who.int/foodsafety/publications/monographs/en/ (accessed on 18 November 2014).

[2] Food and Agriculture Organization of the United Nations. *Residue evaluation of certain veterinary drugs*. Joint FAO/WHO Expert Committee on Food Additives, 78th meeting, 2014, JECFA Monographs 15, FAO, 2014.

[3] WHO Technical Report Series, No. 990 (in press).

[4] For further information on the WHO Food Additives Series, see: http://www.who.int/foodsafety/publications/monographs/en/ (accessed on 18 November 2014).

Significance for public health policies[1]

27. The Committee's work identifies and, if possible, quantifies the public health significance of exposure to chemicals in food, in this case, residues of veterinary drugs, through scientific risk assessment based on international consensus. When a health concern is identified, clear recommendations are issued for action by national governments or through the FAO/WHO Food Standards Programme (i.e. the Codex Alimentarius Commission and its subsidiary bodies).

28. All Member States face the problem of assessing potential risks of chemicals in food, however, only a few scientific institutions systematically assess, on a national or regional basis, all relevant toxicological, epidemiological and related data. It is therefore important that the present report provides Member States with valid information on both the general aspects of risk assessment and the specific evaluations of those veterinary drugs, food additives and food contaminants mentioned. The Committee's work, in its complexity and in reaching an international consensus on the evaluation of these compounds, is unique in its importance for and impact on global public health decisions related to food safety.

29. The Committee's recommendations are used by the Codex Alimentarius Commission in the development of international food safety standards and other guidance and recommendations. Such standards are science-based and are established only for substances that have been evaluated by the Joint Expert Committee. This ensures that the international trade of food commodities meets strict safety standards, to protect the health of the consumer and ensure fair practices in food trade.

30. The advice provided by the Committee is also considered by Member States directly when national or regional food safety standards are being established.

Implications for the Organization's programmes[1]

31. The evaluation of chemicals in food by the Committee is an ongoing activity. Three meetings of the Joint FAO/WHO Expert Committee on Food Additives were planned and implemented in 2012–2013: two were held on food additives and contaminants, one in June 2012 and another in June 2013; another on the evaluation of residues of veterinary drugs in food was held in November 2013. For 2014–2015, three meetings are scheduled: one was held in June 2014 and two are planned for 2015.

32. WHO is a partner in the Joint FAO/WHO Food Standards Programme, whose principal organ is the Codex Alimentarius Commission. In its capacity to assure the sound scientific basis for international standards and recommendations on food additives and contaminants in food, the Joint FAO/WHO Expert Committee on Food Additives provides information that is crucial to the work of the Codex Alimentarius Commission.

33. The Committee's evaluations are also made use of by WHO Representatives and in regional offices when advice is provided to Member States on food safety issues.

[1] This section is relevant to both meetings.

Report of the seventh meeting of the WHO Study Group on Tobacco Product Regulation[1] Rio de Janeiro, 4–6 December 2013

34. The WHO Study Group on Tobacco Product Regulation has launched a series of reports to provide a scientific foundation for tobacco product regulation. In line with Articles 9 and 10 of the WHO Framework Convention on Tobacco Control,[2] these reports identify approaches to underpin the regulation of tobacco products. Such products pose significant public health threats and raise questions on tobacco control policy.

35. The seventh meeting focused on issues critical to advancing the regulation of tobacco products, particularly as outlined at the fifth session of the Conference of the Parties to the WHO Framework Convention on Tobacco.[3] The topics discussed included the evolution of novel tobacco products and other related ones; smokeless tobacco; reduced ignition propensity cigarettes; nicotine reduction and addictiveness; and a non-exhaustive priority list of toxicants.

Novel tobacco products

Main recommendations

36. A tobacco product is considered novel if it contains tobacco and if at least one of the following applies: (a) it has been on the market for less than 12 years; (b) it has been on the market for a longer time but with market share increases in countries or regions that traditionally did not use the product; (c) it uses a new technology; and (d) it is marketed as being less hazardous to health than other tobacco products.

37. Novel tobacco products should be evaluated for toxicity, disease risk, consumer awareness and perception, pattern of use, and product usage demographics. A standardized evaluation of such products is needed and regulators should approve them only if pre-market testing shows a potential public health benefit. The concept of "harm reduction" used by the industry, and the impact and effectiveness of strategies promoting the use of products that are allegedly less hazardous to health, should be evaluated and communicated effectively to the general public in order to prevent misperceptions.

Significance for public health policies

38. The major concerns relating to the use of novel tobacco products include unrecognized toxicity, increased or sustained prevalence of tobacco use, misconceptions about what makes a product less hazardous, and "dual-use" consumption.[4]

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[1] WHO Technical Report Series No. 989 (in press).

[2] For more information, see: http://www.who.int/fctc/text_download/en/ (accessed 28 November 2014).

[3] For more information on the Conference of the Parties to the WHO Framework Convention on Tobacco, see decision FCTC/COP5(6), paragraph 3(b) and decision FCTC/COP5(10), paragraphs 1–4, at: http://www.who.int/fctc/cop/en/ (accessed 28 November 2014).

[4] The concomitant use of two forms of tobacco is an increasing public health concern. As yet, however, there is little consensus regarding a consistent definition of such "dual use". For present purposes, the term refers to cigarette and smokeless tobacco consumption, or cigarette and a novel tobacco product consumption, with either product used daily or nondaily.

Implications for the Organization's programmes

39. It is essential that the approach to monitoring be more comprehensive and consistent, and that the collection of research data on novel tobacco products be more systematic.

Smokeless tobacco

Main recommendations

40. Clearer policy is required to address the challenges presented by smokeless tobacco products. In comparison with their counterparts (i.e. smoked tobacco products), smokeless tobacco products are more affordable, they carry weaker warning labels, and there are fewer resources spent on their surveillance, prevention and control. Evidence-based control policies must be strengthened, such as ensuring disclosure of product content, establishing performance standards for toxicants and maximum pH levels, banning flavourants, establishing effective and relevant health warning labels, increasing product taxes, restricting or banning marketing of such products, and increasing public awareness of harm associated with their use.

Significance for public health policies

41. Increased attention must be given to the overall impact of smokeless tobacco products, including their use by adolescents, dual use, poly use, and the growth in targeted marketing of them for indoor use.

Implications for the Organization's programmes

42. Additional data are needed on usage, surveillance and characteristics of smokeless tobacco products, as well as on the health consequences relating to the use of different ones. Further, it is important to have an understanding of the market for such products and an insight into the measures in place with respect to effective region-specific education, prevention and treatment interventions. Resources and collaborative work are needed in order to obtain such data.

Reduced ignition propensity cigarettes

Main recommendations

43. Technology used in cigarette manufacturing that reduces the fire-starting risk is referred to as reduced ignition propensity ("RIP"). Laws relating to reduced ignition propensity have now been enacted in Australia, Canada, South Africa, the United States of America, and the European Union, but this pattern has yet to be followed in many middle- and low-income countries. The ideal is the universal application of this technology to cigarette manufacturing; to achieve this, testing must be standardized in accredited laboratories and paid for by the tobacco industry. However, claims of a reduced risk to health should not be allowed. Monitoring is needed to establish whether such technology has an impact, in particular whether it can be shown that there is a reduction in fires, deaths and injuries related to cigarettes that use this technology. Health correlates should be monitored for toxicity and for behavioural changes related to a heightened awareness of reduced ignition propensity in cigarette manufacturing.

Significance for public health policies

44. Fires caused by smoking are a major public health risk and cause many deaths. A reduction of approximately 30% in smoking-related fires has been shown in areas with reduced ignition propensity laws. Testing has not shown any difference in smoke emissions between cigarettes that have been manufactured using reduced ignition propensity technology and those that have not. These findings refute the claims of the tobacco industry.

Implications for the Organization's programmes

45. More research is needed on toxicity, emissions, possible changes in smoking behaviours related to reduced ignition propensity cigarettes, and evaluation of the potential reduction in fires and fire-caused deaths.

Nicotine reduction

Main recommendation

46. Reduced nicotine cigarettes are feasible for reducing tobacco addiction, especially in combination with nicotine-based treatment. Switching from conventional to reduced nicotine cigarettes, where the reduced level of nicotine is approximately 0.1 mg nicotine per approximately 1 gram of tobacco, does not lead to a significant increase in craving or to withdrawal symptoms, and does not result in compensatory smoking behaviour (such as a greater intensity of smoking or an increased number of cigarettes smoked per day). A specific amount of nicotine has not yet been identified as an absolute threshold for addiction, however, the level is likely to be less than approximately 0.1 mg nicotine per approximately 1 gram of tobacco. The benefits of such a strategy require: firstly, the replacement, complete or partial, of existing products with reduced nicotine cigarettes; and secondly, the implementation of steps to ensure such a replacement programme takes place.

Significance for public health policies

47. A nicotine reduction strategy has the potential to: (a) reduce the acquisition of smoking and progression to addiction among experimenters; (b) reduce the amount of cigarettes smoked among some proportion of addicted smokers as a result of modified behaviour; and (c) support both an increase in the number of addicted smokers who stop smoking and a reduction in the number of those who relapse.

Implications for the Organization's programmes

48. The implementation of a nicotine reduction policy would need to be supported by a comprehensive programme involving:

(a) a strategy on health communication and public education;

(b) treatment that is available, effective and affordable, which includes alternative forms of nicotine;

(c) the capacity to monitor the market and to test products;

(d) continued research to assess:

  (i) likely use and effects of reduced nicotine cigarettes among non-smoking adolescents;

(ii) long-term use of reduced nicotine cigarettes;

(iii) long-term impact on smoking behaviours.

Non-exhaustive toxicant list of contents and emissions of tobacco products

Main recommendation

49. Among the chemicals found in cigarette smoke (as many as 7000), the WHO Study Group on Tobacco Product Regulation identified a non-exhaustive priority list of 39 tobacco contents and emissions of cigarette smoke. Criteria included toxicity potential for smokers and variability of concentrations between different cigarette brands. The Study Group concluded that measurement of tar was uninformative.

Significance for public health policies

50. Monitoring the non-exhaustive toxicant list will eventually guide the regulation of contents and emissions, as stated in Articles 9 and 10 of the WHO Framework Convention on Tobacco Control. This priority list should be periodically re-evaluated as new knowledge becomes available.

Implications for the Organization's programmes

51. Any monitoring and regulation of contents and emissions should be done in conjunction with the existing validated methods of the WHO Tobacco Laboratory Network. Currently, laboratories in the Network have already validated tar, nicotine, carbon monoxide, tobacco-specific nitrosamines, benzo[*a*]pyrene, and humectants. Validations for ammonia, volatile organic compounds and aldehydes are ongoing. Among non-existing methods, priority should be given to laboratories in the Network for their development of standardized testing methods for the measurement of cadmium and lead in tobacco contents, nicotine in the smoke of waterpipes, and nicotine, tob acco-specific nitrosamines and benzo[*a*]pyrene in smokeless tobacco products.

ACTION BY THE EXECUTIVE BOARD

52. The Board is invited to note the report.

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