

Modernizing methodology for the WHO assessment of substances for the international drug control conventions

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ABSTRACT

Background: The WHO Executive Board revised the guidance that governs the procedures for the WHO review of psychoactive substances for international drug control in 2010. To meet the standards defined in these guidelines, the current evaluation methodology at WHO must be an evidence-based assessment.

Methods: We describe the history of substance evaluation from 1912 to the present and the development of the evaluation methods over time including a description of the current assessment system, using reports from WHO and its predecessor, the League of Nations. Furthermore, we describe the current review system.

Results: We found that some substances under international control were never reviewed; other substances were reviewed decades ago.

Conclusions: We argue that assessments do not have unlimited validity, and therefore, substances need to be re-assessed periodically, as already recommended by the Expert Committee on Drug Dependence in 1982. We propose that the evaluation time be shortened; that the influence of the route of administration and/or dosage form of the preparation is considered in the evaluation; and we recommend studying national and regional assessment systems and adopting their best practices. With this article, we make a case for the inclusion of systematic review and other methods of comprehensive analysis of substance evaluation to arrive at a process of equal rigour and quality as already applied by WHO for the development of treatment guidelines.

Keywords: Drug evaluation, History, Evaluation methods, World Health Organization, League of Nations

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1. Introduction

The year 2012 was the centenary of international drug control. On 23 January 1912, twelve countries (China, France, Germany, Great Britain, Persia (now Iran), Italy, Japan, the Netherlands, Portugal, Russia, Siam (now Thailand) and the United States of America) agreed on an Opium Convention in The Hall of the Knights in The Hague, The Netherlands (League of Nations, 1922). Over the years, various other conventions expanded the scope of this first international treaty on drug control and currently three international drug control conventions are in force: the Single Convention on Narcotic Drugs, 1953, as amended by the 1972 Protocol amending the Single Convention on Narcotic Drugs, 1953; the Convention on Psychotropic Substances, 1971; and the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988 (United Nations Treaty Collections, *sa*; United Nations Office on Drugs and Crime, 2009). Today, these three conventions have been widely adopted with almost all States being a party to the treaties: as per 1 November 2010, eight countries are not party to the 1953 Convention, 11 not to the 1971 Convention and 10 not to the 1988 Convention.

The Single Convention and the Convention on Psychotropic Substances charged the World Health Organization (WHO) with the evaluation of substances that potentially could be brought under the scope of these two conventions. WHO substance evaluation has evolved and in its 126th Session in January 2010, the WHO Executive Board adopted a revision of earlier guidance documents (World Health Organization, 2010). This guidance document mainly regulates the assessment procedures by WHO's Expert Committee on Drug Dependence (ECDD) including aspects of transparency, publication procedures and confidentiality. It provides algorithms for certain scheduling situations for which no guidance was given previously. Although it requires evidence-based assessment and mentions the topics to be discussed in the substance specific Critical Review Report (which serves as the basic document for the Expert Committee session), the methodology as to arrive at an evidence-based assessment is not described. Therefore, in order to meet the quality level required by the Executive Board in the Guidance for the WHO Review of Psychoactive Substances for International Control, there is a need to define and develop more accurate evaluation methods.

This article describes the history of international substance evaluation, determines how the substances that are now under control were assessed, identifies the need for further developing evidenced-based WHO assessment, and explores possibilities to apply this methodology.

2. History of international substance evaluation

2.1 Review by the League of Nations

For the administration and implementation of the first treaty of international drug control, the 1912 International Opium Convention, the Netherlands acted as the

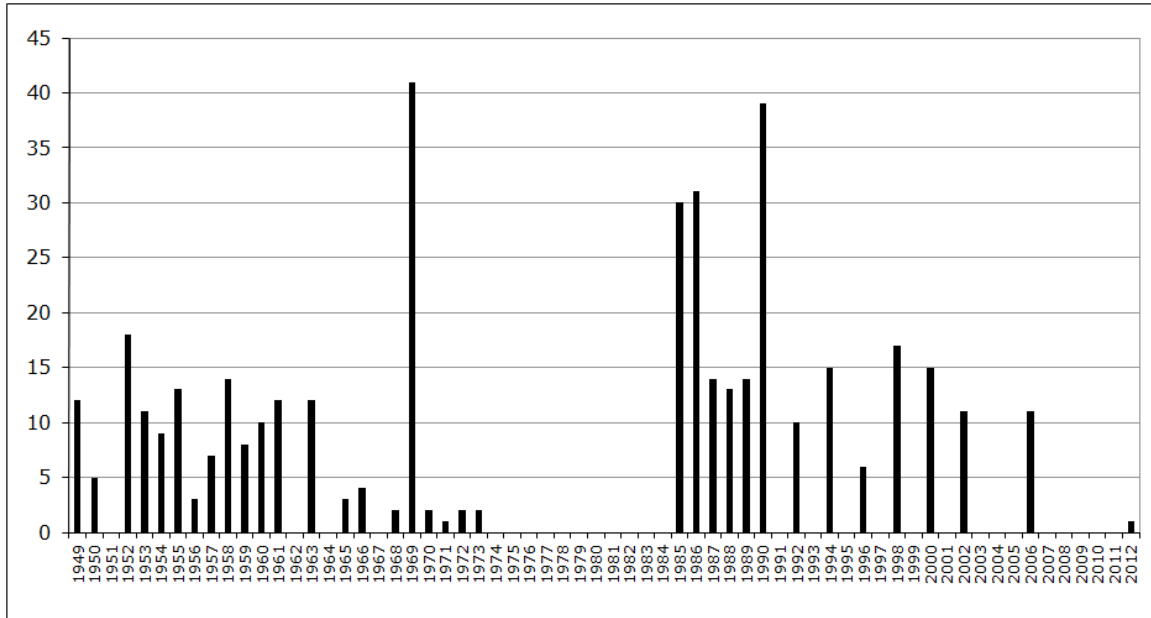
responsible overseeing agent. When after the 1st World War, in 1919, the League of Nations was established, it was accepted that this international agency would take over the functions laid down in the 1912 convention (League of Nations, 1920). Under the auspices of the League of Nations, a Health Committee was formed. From 1920 to 1940, this committee of experts determined which new substances should be controlled internationally, based on recommendations by the Paris-based International Office for Public Health (Office international d'Hygiène publique, 1921-1939). In 1912, four substances were placed under international control: opium, cocaine, morphine and heroin. When the 1925 International Opium Convention came into effect in 1929, it broadened its scope by adding several substances: “Indian hemp” (cannabis), its resin and its Galenic preparations, crude cocaine, coca leaf, ecgonine and all ester derivatives of heroin, cocaine and morphine. (League of Nations, 1925). Furthermore, the concept of group control was introduced: all esters of morphine fell under the scope of control in order to pre-emptively protect against equally harmful derivatives. It provided, under article 10, terms for the addition of new similar substances after the Convention had been concluded, introducing the concept of constant drug review. In the years following the adoption of this convention, a total of ten emerging drugs were added with article 10. The subsequent 1931 Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs proposed strict drug production regulation. 78 substances were added to this 1931 Convention. (League of Nations, 1932)

2.2. *Review by the WHO (1948-present)*

In 1948, after the UN took over the role of the League of Nations, WHO took upon the tasks from both the Health Committee and the Office international d'Hygiène publique. From 1949 to 1965, the Expert Committee worked under various other names and occasionally also various other groups were convened to review or to discuss specific topics. (See Table 1). Since 1949, the WHO Expert Committee on Drug Dependence (ECDD) and WHO ad-hoc committees on drugs (1978 – 1985) have discussed 703 substances and 257 preparations. Since 1948, they made 553 recommendations of which 547 related to scheduling (Figure 1). All Expert Committee Reports can be searched for in the WHO Library Database (<http://apps.who.int/iris>). ECDD and related reports are also listed at the WHO Medicines/Controlled Substances website.

Through examining the expert reports we found that 28 internationally controlled substances were never reviewed by the WHO. To extend this further in time; 3 from these 28 substances (cocaine, opium and morphine) were never reviewed by the League of Nations in the period after their inclusion in the 1912 Opium convention; cannabis resin was not reviewed after its inclusion in the 1925 convention. Although the Expert Committee stated in its ninth report that it “believed that the composition of the schedules

Fig. 1. Number of ECDD substance recommendations on drug scheduling from 1948 to the present.



[on the draft list for the Single Convention] should be most carefully reviewed before they become an established part of the new Convention” (World Health Organization, 1959), its tenth report only mentions that substances in Schedule III were reviewed individually, whilst the other Schedules seem to have been a quick review of the lists with a few remarks to move substances to other Schedules. (World Health Organization, 1960).

Table 1 shows the year(s) of recommendation for selected substances that are important for medicine and/or misuse potential. Additionally, the year of the most recent evaluation by the WHO is listed for these selected substances. For use in this table, "evaluation" is defined as a mere discussion of the properties of the substance, without a formal decision to make a recommendation.

Table 2 lists the major events in international substance evaluation since WHO became responsible for substance review. It represents a number of major events since the period that WHO took responsibility for international substance evaluation. Experts discussed the review methods on many occasions, with several meetings mainly or

Table 1.

Last year of review (1912 - present) of selected substances important for medicine and/or misuse potential.

Substance	League of Nations (1919-1948)	WHO ECDD (1948 - present)	
	Year(s) of recommendation	Year(s) of recommendation	Year of most recent evaluation (not leading to a recommendation)
Amphetamine	-	1969	-
Cannabis	1924, 1935	-	1965
Codeine	1935	-	-
Diazepam	n/a ^a	1969, 1982, 2000	-
Hydrocodone	1926, 1937	1949	1955
Hydromorphone	1929, 1937	-	-
Lysergic Acid	-	1969	-
MDMA	-	1985	-
Mescaline	-	1969	1964
Methadone	-	1949	1968
Phenobarbital	-	1969	1977
Coca leaf	1935	-	1965
Psilocybin	-	1969	-
Oxycodone	1926, 1937	-	1954
Heroin	1935	-	1949

exclusively on methodology (World Health Organization, 1975, 1978, 1981). Initially, barbiturates (1952) and amphetamines (1953) were reviewed as a class. After 1953, the ECDD evaluated substances individually, even when similar substances were on the agenda simultaneously. The current scheduling of the barbiturates is based on a later individual review (World Health Organization, 1987).

^a Did not exist at the time

Table 2.
Milestones in WHO drug evaluation.

Year	Event
1948	WHO assumed responsibility for drug convention regulation and substance evaluation.
1948 - 1955	Expert Committee on Habit-Forming Drugs.
1955 - 1964	Expert Committee on Drugs Liable to Produce Addiction.
1961	Single Convention on Narcotic Drugs.
1964 - 1968	Expert Committee on Dependence Producing Drugs.
1964	The Single Convention came into force.
1968 - present	Expert Committee on Drug Dependence.
1969	Original list of substances proposed for inclusion into the 1971 Convention reviewed. (World Health Organization, 1970).
1971	Convention on Psychotropic Substances.
1974	A WHO Scientific Group on Evaluation of Dependence Liability and Dependence Potential of Drugs reviewed new substances for inclusion in the schedules. Additionally it initiated more precise rules for formulating WHO recommendation on inclusion of new substances into the schedules (World Health Organization, 1975)
1976	The 1971 Convention came into force.
1978 - 1985	WHO ad-hoc committee on drugs met eight times to consider various aspects of the implementation of the 1971 convention.
1980	WHO Expert Committee on Implementation of the Convention on Psychotropic Substances, 1971, described techniques for assessment of public health and social problems associated with the use of psychotropic drugs. (World Health Organization, 1981)
1982	WHO Review Group recommended 33 benzodiazepines for Schedule IV of the 1971 Convention without ECDD involvement (World Health Organization, 1982).
1986	The first formal Procedure for the WHO Review of Dependence-Producing Psychoactive Substances for International Control was established (World Health Organization, 1986)
1988	ECDD requested the development of additional procedural guidelines for the review of substances already under international control (WHO Expert Committee on Drug Dependence, 1988)
1990	WHO Executive Board revision of the Guidelines; introduction of the pre-review and critical review. (World Health Organization, 1990)
1994, 1999 and 2000	More WHO Executive Board revisions of the Guidelines. (World Health Organization, 1994, 1999, 2000)
2004 and 2005	Proposals for Supplementary guidelines containing guidance concerning the choice between the three conventions were rejected (World Health Organization, 2004, 2005)
2010	The WHO Executive Board adopted the current version of the ECDD guidance. (World Health Organization, 2010)

3. Current review system by the WHO

After the WHO Executive Board rejected proposals for Supplementary guidelines twice (World Health Organization, 2004, 2005), the Secretariat developed a major revision of the guidelines in force, addressing the issues that the Supplementary guidelines were supposed to address, but also paying attention to transparency of the process and the use of the internet. With the adoption of the Guidelines for the WHO Review of Psychoactive Substances for International Control by the Executive Board, the procedures to follow by the ECDD for abuse liability assessment are clearly defined and it requires that the approach is evidence-based (World Health Organization, 2010). The procedure is centred around matters of public health to consider if a substance should be placed in the Single Convention on Narcotic Drugs, 1961 (Schedule I or II) or the Convention on Psychotropic Substances, 1971 (Schedule I, II, III or IV). Evaluation of a substance is undertaken by the ECDD and utilizes data provided by the WHO Secretariat. Overall, the review procedure considers a substance's similarity to substances already in the 1961 or 1971 Conventions as well as a substance's degree of therapeutic usefulness and impact on public health through its liability of abuse. The procedure involves a pre-review and critical review.

A pre-review is initiated when proposed by the Secretariat or any member of the Expert Committee or invited participant in the Committee meeting, along with supporting information. Pre-review of a substance is a preliminary analysis and determines whether current information justifies an Expert Committee critical review or not, with no further evaluation. Such information is based on categories identical to those used for the critical review procedure (below) but provided by the Secretariat in the form of a brief summary.

A critical review of a substance utilizes assessment by the Committee of comprehensive data with the purpose of advising the Director-General to recommend its scheduling (or not), or to amend the scheduling status in the 1961 or 1971 Conventions. Critical review is initiated when i) there has been notification from a Party to the 1961 or 1971 Convention, or ii) there has been an explicit request for review from the Commission for Narcotic Drugs, or iii) the pre-review of a substance by the Expert Committee has recommended a critical review, or iv) information is brought to WHO's attention that a substance is clandestinely manufactured, of especially serious risk to public health/society, and is of no recognized therapeutic use by any Party (but if therapeutic use is identified then the substance shall be subjected to pre-review).

The critical review documentation produced and collated by the Secretariat includes questionnaire responses of request for information from Member States and drug control bodies, as well as relevant information under the following headings:

- 1) substance identification,
- 2) chemistry,
- 3) ease of convertibility into controlled substances,
- 4) general pharmacology,
- 5) toxicology,
- 6) adverse reactions in humans,
- 7) dependence potential,
- 8) abuse potential,
- 9) therapeutic applications,
- 10) listing on the WHO Model List of Essential Medicines,
- 11) marketing authorizations as a medicine,
- 12) industrial use,
- 13) non-medical use, abuse and dependence,
- 14) nature and magnitude of public health problems,
- 15) licit production, consumption and international trade,
- 16) illicit manufacture and trafficking,
- 17) current international controls and their impact,
- 18) current and past national controls, and
- 19) other relevant medical and scientific matters.

When reviewing the substances on the agenda for the 34th and 35th ECDD, the Committee also included in its considerations under item 19 the currently relevant and more pronounced importance of the consequences of scheduling for accessibility of medicines made from controlled substances, like long-acting opioids for the treatment of dependence, or opioid analgesics (World Health Organization, 2012a).

4. The future of the evaluation methods

4.1. Meeting the new EB requirements

As mentioned, the newest version of the ECDD guidance explicitly requires the evaluation of substances to be grounded in an evidence-based approach. Expert-reviewers should present the data in the critical review in a manner that will facilitate an evidence-based assessment by the Expert Committee and should allow for an evaluation of the strength of evidence.

Although the critical reports prepared by the Secretariat until today provide a comprehensive overview of the data available and are therefore not devoid of an evidence-base, they are rather an enumeration than a systematic review. The WHO substance evaluation could gain considerably from the introduction of a mandatory systematic review of the literature by using the GRADE methodology (Atkins et al, 2004) on several aspects of the procedure. For instance, the WHO therapeutic guidelines have undergone considerable improvement through such an introduction (World Health

Organization, 2012b). The GRADE approach involves assessing the quality of evidence on a particular question, taking into consideration the magnitude of the effect, the relevance of the data to the clinical question being asked, the sample size in the relevant trials, the methodology of the trials, and the consistency of the findings. To produce a series of recommendations, the technical experts consider the evidence from reviews and meta-analyses, whilst taking into consideration evidence from other sources, technical considerations, resource implications, and the risks and benefits of different alternatives. The strength of each recommendation comes from considering the effectiveness of the intervention, the strength of the evidence, the resource implications, the balance between benefits and harms, and finally, a consideration of ethical implications. Items for which the quality of the evaluation could benefit from such an approach are e.g. items 5-7, 13 and 14 as mentioned above. For qualitative information required by the guidance, a systematic review cannot easily lead to conclusions (e.g. 3). In other cases much will depend on data availability (e.g. 8): for older substances a systematic review may be possible, but usually hardly any data are available for the many newer substances that need to be reviewed.

For topics where a systematic review is not possible, we propose a Delphi approach (Linstone and Turoff, 1975; Iqbal and Pison-Young, 2009). The available information will be presented to the experts several months in advance of the meeting. They will rate anonymously the relevance and seriousness of the problems related to the substance under review and submit their arguments for their ratings. All submitted arguments will be presented in a similar second round for which the outcomes will be presented to the ECDD. This process contributes to a reasonably high level of common understanding among the Experts based on shared information. Expert Committee decisions on these topics will be based on a high level of information. Finally, for several other items the usual listing or description in the critical review report remains sufficient (e.g. 1, 2, 10, 11 and 12).

4.2. Temporal aspects of the review

The present situation in which several important substances (e.g. cannabis, cannabis resin, heroin and cocaine) were never evaluated or were evaluated up to eight decades ago seriously undermines and delegitimizes their international control. In addition, their historic evaluation no longer represents current scientific information.

As clarified above, the assessment methods have changed considerably over time. Moreover, epidemiological aspects related to abuse liability are not constant (e.g. availability, cost, extent of actual abuse, sociological aspects) and require periodic re-evaluation. A regular re-assessment is necessary for establishing the uninterrupted validity of drug control. The ECDD already recommended the WHO to develop procedural guidelines to implement a regular re-evaluation in its 25th report of 1982. The

authors of this article propose that any substance under control should be re-assessed at least every twenty years.

Furthermore, the guidance document requires an Expert Committee to be held every second year. Subsequently, the addition to the convention of a substance through a pre-review and a critical review will usually take four years from the initiative to review until the moment of scheduling at the country level. Such a delay is long compared to the rapid developments related to substance misuse and can cause countries to take their own initiatives for scheduling, resulting in confusion in international trade and problems with mutual legal assistance. Moreover, countries with low resources are often dependent on a WHO recommendation and a consecutive scheduling decision by the UN Commission on Narcotic Drugs for their national scheduling decisions. Considering the same type of data are used for assessment in both the pre-reviews and the critical reviews, abolition of the pre-review stage will lead to a shortening of the procedure by around two years. Alternatively, formatting of the pre-review using internet technology might allow for conducting this step in between meetings, thus speeding up the process.

4.3. Pharmacokinetics as a consideration for re-assessment

Unlike in the early days of substance evaluation, scientists today are aware that dependence-producing properties are not only a function of the substance, but also include the route of administration and the dosage form. Therefore, dependence liability may vary for the various preparations of the same substance. The rewarding properties of an injected substance are usually greater than that of a slow-release preparation, based on the fact that the former reaches the brain very fast and the latter may take hours before the psychotropic action sets in. It may be worthwhile that the ECDD considers what this means for drug control when re-evaluating major medicines. This is of particular importance for public health, because it has been shown that drug control can impede access to controlled medicines (De Lima L et al., 2001; Cherny NI et al., 2010)

4.4. Incorporation of best practices

Several countries have developed comprehensive assessment procedures for their national purposes, or like in the European Union, there is a joint assessment mechanism through the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). At the country level for example, the Netherlands has set up a drug detection and assessment system (CAM), active since 1999 to carry out a risk assessment on all new drugs, new combinations of drugs or new applications of existing substances that have appeared on the market. This risk assessment considers the risk both to public health and to public order and safety using a non-anonymous Delphi method (Van Amsterdam et al., 2004). Nutt et al. (2007) suggested a new system for assessing the potential harms of individual

drugs on the basis of fact and scientific knowledge using a Delphi method and a nine-issue matrix. Comparing these various methods and including best practices in the WHO review may further enhance this review.

Please see Table 3 for a listing of the recommendations presented in this Section 4.

Table 3.

Recommendations for improving WHO's substance evaluation process

Number	Recommendation
1	Introduce a systematic review using the GRADE methodology for aspects of the critical review where this is appropriate. (Section 4.1)
2	Introduce a Delphi survey for aspects of the critical review where a systematic review is not possible. (Section 4.1)
3	Re-assess all substances scheduled in the Single Convention and the Psychotropic Substances Convention at least every twenty years, starting with the most relevant substances cannabis, cannabis resin, some amphetamines, heroin and cocaine. (Section 4.2)
4	Consider possible ways to speed up the assessment process, such as the abolition of the pre-review or conducting the pre-review in between Committee meetings using the Internet. (Section 4.2)
5	Consider if the differences in rewarding properties resulting from pharmacokinetic properties of the preparations within one substance can be a reason for different levels of control (Section 4.3)
6	Consider the assessment procedures used elsewhere and adopt best practices from these procedures. (Section 4.4)

5. Discussion

5.1. *Resume*

We made an inventory when substances under international drug control were reviewed since the first Opium Convention was agreed on in 1912. We found that cocaine, opium and morphine were never scientifically evaluated in the century that drug control exists now, 25 more were not evaluated since WHO took over from the League of Nations and many others were not reviewed for decades, e.g. cannabis not since 1965. Then, we discussed the WHO assessment as it is currently in place.

The WHO Recommendations for scheduling decisions for the international drug control conventions should be prepared with equal rigour and quality control as applied to formally approved WHO treatment guidelines; including evidence based systematic reviews for medical and pharmacological aspects, and Delphi analyses for maximal

expert consent on qualitative aspects. The decisions of the members of the ECDD should not be based on personal views, experiences or anecdotes, but rather systematic reviews and comprehensive analysis wherever possible.

Assessments do not have unlimited validity, and therefore, substances need to be re-assessed periodically. Legitimacy of international drug control depends on many factors and one factor is the scientific evaluation of the substances under control: “Is there a good reason to control these substances?” Like the ECDD stated in 1982, we recommend that any substance under international control is re-assessed regularly and we propose that this be at least once in twenty years.

Other improvements needed in the WHO assessment are: (1) shortening the time between the moment a problem is raised until the recommendation is included in the treaty and implemented by the country; (2) taking pharmacokinetics of preparations into account for scheduling recommendations; and (3) to study national and regional assessment systems for copying their best drug evaluation practices.

5.2. *Study limitations*

In order to assess the number of substance evaluations, we tried to determine as unambiguously as possible whether a mention of a substance is related to an assessment. For the 1912 Opium Convention, we can only speculate that there was a common political feeling that morphine, opium and cocaine should be scheduled; we have no proof of a scientific assessment. Thereafter we found straightforward reports from the Health Committee of the League of Nations and the World Health Organization. During the early years of the World Health Organization, some reports were ambiguous and for some recommendations it is clear that these were not related to an assessment, e.g. the recommendation not to use heroin as an analgesic, repeated in several consecutive meeting reports. Another example was the way the Expert Committee reviewed the list of substances to include in the proposed schedules of the Single Convention as mentioned above. Whenever it was obvious that there was no real and individual assessment, we did not count such a recommendation. From the moment that the ECDD distinguished between pre-review and critical review (i.e. in its 28th meeting, 1992), we counted the latter. For these reasons, others might make other choices and might find slightly, but not substantially, different numbers of substance evaluations.

5.3. *Implications of our recommendations*

If our recommendations for improving WHO substance evaluation are put into practice, this will lead to an increased quality of the assessment and more speedily available outcomes. Conducting systematic reviews, Delphi studies and re-assessments every twenty years will increase the cost of assessment indeed, however, these cost are negligible compared to the expenses on drug control around the world. Even a minor shift of countries' drug control budgets towards the WHO substance evaluation will be

sufficient. Such an investment will repay in our view and will action a more realistic scheduling for certain substances,. The scheduling of cannabis is an example of such a potential improvement: currently it is in Schedule I, but also in Schedule IV. Substances in Schedule IV have according to the Convention “particular dangerous properties” and do not have any other use than in medical and scientific research. Although this may have been true in the past, it is not true anymore in the 21st century.

It is not certain that the Commission on Narcotic Drugs will adopt all WHO’s recommendations; for instance it rejected WHO’s 2006 recommendation to reschedule dronabinol. But assumed that the CND let the scientific approach prevail over political considerations, such an update to modern knowledge will accommodate for the moment those countries that are uncomfortable with the current international drug control arrangements, although it will not address the more structural criticism related to the prohibition principle. In practice, a process of turning away from international drug policies by individual countries has started already. The clearest example is Bolivia by having a reservation now for the control of coca leaf.

5.4. Conclusion

Despite that there is hardly any debate whether populations and individuals should be protected against the potential harms of drugs, the international drug control system has been challenged by many for its actual effects, both in terms of its effectiveness for achieving its objectives and for its unintended side effects. With this article, we do not discuss the question whether the current system is appropriate or effective, but we contend that, as long as the current system is in place, decisions on the scheduling of substances in the international drug control Conventions should be based on high quality scientific assessments relevant to the time of review. We showed that whilst this is not presently the case, it is feasible for the future.

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Contributors

ED investigated the archives of the League of Nations and wrote the first draft of the manuscript. LAS made an inventory of the reviews in the WHO Expert Committee reports. WW provided the information for Table 2. ED and WKS edited the final version of the manuscript. WKS coordinated the project. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Nothing declared.

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