Spice phenomenon – difficult questions for drug monitoring and policy

Risk Assessment Guidelines

Dr. R. Sedefov, Lisbon, 15 June 2009
This presentation

Part 1: Spice phenomenon – difficult questions for drug monitoring and policy

Part 2: Risk Assessment Guidelines
The request

‘During the meeting, some delegations alerted about the growing phenomenon of herbal mixtures on sale via the Internet, some of them probably including with chemical substances ('spice' or 'legal highs').

It was decided that the EMCDDA will launch a survey among Reitox national focal points on this issue. Furthermore, the Management Board decided to ask the Scientific Committee to analyse the matter.

I would be grateful if you could include this item on the agenda of the next meeting of the Scientific Committee and report back to me on the conclusions of the discussions.’
The story of Spices…

- Herbal mixtures sold on the Internet and specialised shops.
- An ‘exotic incense blend’ (‘not for human consumption’) or a ‘smoking mixture’.
- Reported by some users to have effects similar to cannabis.
- Extensive forensic investigations by some Member States identified synthetic cannabinoids added to the herbal mixture (JWH-018 and CP).
- Mainly an Internet phenomenon, but also smart and head shops.
- Control measures: Austria, Germany, France, Luxembourg, Poland.
- New cannabinoids continue to appear (JWH-073).
Purported product design

Some of the declared ingredients are said to produce cannabis-like effects:

- Canavalia maritima (‘Baybean‘)
- Pedicularis densiflora (‘Indian Warrior‘)
- Leonotis leonurus (‘Lion’s Tail‘)
- Zornia latifolia (‘Maconha Brava‘)
- Leonurus sibiricus (‘Siberian Motherwort‘)
Examples (many now obsolete)
Cannabinoid receptor agonists

Endogenous: anandamide and four closely-related structures

Exogenous:

(i) phytochemicals, e.g. Δ⁹-THC
(ii) synthetic substances

1. Analogues of Δ⁹-THC (e.g. HU-210, Nabilone)

2. Cyclohexylphenols (Pfizer CP-compounds)

3. Naphthoylindoles (JWH compounds)

4. Others (naphthoylpyrroles, naphthylmethylindoles, naphthylmethylindenes, phenylacetylimidoles, fatty acid amides?)
Cannabinoid receptor agonists 2

- Synthetic CB$_1$/CB$_2$ agonists fall into various chemical groups
- There are many known examples in each group
- They are small molecules (typically 20-26 carbon atoms)
- They are lipid-soluble and non-polar
- Many are much more potent than Δ$^9$-THC
- Their detailed pharmacology has not been investigated

It follows that:
- They are fairly volatile (and hence ‘smokable’)
- Typical doses may be less than 1mg
- They will present analytical, toxicological and legal challenges
Why did it take such a long time?

• The content (design) of the Spice products.

• Legal sales of Spice products as a commodity via the Internet or in specialised shops, rather than clandestine production and illegal circulation as a drug did not generate seizures or criminality that might have prompted the interest and involvement of specialised law enforcement agencies.

• Thus the distribution and sale of these products took place in a ‘grey zone’ where the potentially responsible institutions (law enforcement bodies, public health authorities, consumer protection agencies or the competent authorities for medicinal products) did not assume direct responsibility.

• Conceptual problem reflecting the lack of consensus on how this type of product should be viewed.
Are those products dangerous for the consumer?

- No pharmaceutical product has emerged, no human studies carried out.

- Little is known about metabolism and toxicology. The synthetic cannabinoids have only been tested in the laboratory (*in vitro* or in animals), the health risk of the inhaled smoke is unknown.

- In the case of JWH-018 it can be assumed that due to structural features there may be a certain carcinogenic potential?

- Active in low doses; accidental overdosing with a risk of severe psychiatric complications because the type and amount of cannabinoid may vary considerably.

- In general, there may be a risk for the appearance of a full CB receptor agonists; leading to life threatening conditions if overdosed?

- Seems that tolerance may develop fairly fast?; arguably this might be associated with relatively high potential to cause dependence.
<table>
<thead>
<tr>
<th>Date</th>
<th>Country</th>
<th>Law</th>
<th>Substance / Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct 08</td>
<td>UK</td>
<td>Pharm</td>
<td>Spice Gold</td>
</tr>
<tr>
<td>7 Jan 09</td>
<td>AT</td>
<td>Pharm</td>
<td>Smoking mixes containing JWH-018</td>
</tr>
<tr>
<td>22 Jan 09</td>
<td>DE</td>
<td>Drug (Temporary)</td>
<td>JWH-018, CP 47,497 (x4)</td>
</tr>
<tr>
<td>24 Feb 09</td>
<td>FR</td>
<td>Drug</td>
<td>JWH-018, CP 47,497 (x4), HU-210</td>
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<tr>
<td>3 Mar 09</td>
<td>AT</td>
<td>Pharm</td>
<td>Smoking mixes containing CP 47,497 (x4), HU-210</td>
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<tr>
<td>9 Mar 09</td>
<td>HU</td>
<td>?</td>
<td>Spice Gold, Diamond, others containing same mixture</td>
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<tr>
<td>20 Mar 09</td>
<td>PL</td>
<td>Drug</td>
<td>JWH-018, several of the supposed herbal ingredients</td>
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<tr>
<td>20 Apr 09</td>
<td>LU</td>
<td>Drug</td>
<td>JWH-018, CP 47,497 (x4), “and other synthetic agonists of cannabinoid receptors”</td>
</tr>
</tbody>
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HU – prohibits using two plants in food supplements
EMCDDA actions (1)

- ‘Spice’ formally monitored since the beginning of 2008; Spice products noted in the EMCDDA Internet snapshot on the availability of legal highs in the beginning of 2008.

- In 2008-2009, the EWS facilitated the exchange of information between the Member States.

- Dec. 2008 a request from the EMCDDA Management Board to the Scientific Committee, hence this presentation.

- Analytical information (from AT, UK, DE, USA) disseminated to the EWS network, ENFSI, etc.

- Substance profiles of Spice, JWH-018 and CP 47,497, etc on the European database on new drugs (EDND).

- On request, the DE and AT legal correspondents provided copies of their respective control decrees.
EMCDDA actions (2)

• January 2009 – EMCDDA launched ad hoc survey amongst the Reitox NFPs (questionnaire).

• February 2009 – an assessment meeting EMCDDA-Europol and brief announcement at the HDG. No action under the Council Decision.


• Meeting report distributed to the Member States (HDG) & Commission on 4 May and published on the EMCDDA website – now a living document.

• EWS network meeting 4-5 June
Council Decision 2005/387/JHA (1)

At present (Feb. 2009) JWH-018, CP 47,497 and its ‘homologs’ do not fulfil the criteria set up by the ‘EWS Operating guidelines’ for the launch of a Europol–EMCDDA Joint Report, because:

- there are no large seizures;
- there is no evidence of international trafficking;
- there is no evidence of organised crime involvement;
- there is little evidence of intoxications and no reported fatalities;
- there is limited information on the toxicopharmacological properties of the substances; and
- there is insufficient evidence about the potential for further (rapid) spread of the substances.

The EWS needs to remain vigilant.
Challenges (1)

‘Herbal highs’ — pose a range of difficult questions for drug control policies:

- Conceptual: how to define which products are of interest;
- Practical and methodological: how to monitor the products sold, identify the synthetic compounds that they may contain and assess their health risks.

Any substance could be added to any herbal mixture, the sheer number of potentially psychoactive synthetic cannabinoids means that control measures targeting individual chemicals can be easily circumnavigated (consider generic approach to control ?).

Little knowledge about the pharmacology, toxicology and safety profile in humans, the type and amount of synthetic substances added may vary considerably and some compounds may be active in very small doses.
Challenges (2): what legislative response?

- Consumer protection
- ‘Spice’ products
- Medicines
- Synthetic cannabinoids
- Drugs
Challenges (3)

Even if control legislation is adopted, the unavailability of analytical data and reference samples, as well as methodologies for toxicological identification of metabolites in urine, are likely to pose challenges to the effective implementation of control measures.

It remains unclear where and how the actual production of the herbal mixtures, the synthetic cannabinoids and their addition to the herbal mixtures takes place.

The extent to which Spice products are used in Europe is unknown and the users seem to be a heterogeneous group. Is there a wider, specific demand for any of these particular substances?

- The EWS is designed and geared towards notification and monitoring of individual substances which is technically a sound practice. Groups of substances (so-called ‘analogues’) cannot be notified and monitored as such.

- Information collection and monitoring, potentially leading to risk assessment(s) should be done separately for each individual substance.

- Notifying and monitoring psychoactive plants may require different reporting approaches: presence of more than one plant material (mixtures), more than one psychoactive ingredient, potency, cultivating, etc.
Anticipating the future

• In the context of fast technological advances, cheap organic synthesis and a global market, synthetic drugs are likely to grow in importance.

• Herbal products, however, will continue to pose specific challenges.

• Internet is likely to continue being the main vehicle.
Conclusion

• We are witnessing a major change in the field of new (‘designer’) drugs due to rapid technological advancement (cheap organic synthesis and Internet) and changed distribution and marketing strategies (‘legal highs’, ‘herbal highs’ ‘research chemicals’, etc.,).

• The EWS is highly operational, but is to a certain extent a reactive tool without a mandate or resources to anticipate and research the future market by actively purchasing, synthesising and studying new compounds.

• Pending decision on the need for further action on synthetic cannabinoids as stipulated by the Decision.
Risk Assessment Guidelines
Risk assessment guidelines

The new guidelines introduce major conceptual and implementation innovations for the risk assessment.

- Adopted by the Scientific Committee during the 29th meeting (17-18 Nov 2008)


- Commission commented (informally, formal letter expected)

‘The Council Decision asks for an assessment of risks, not for a recommendation regarding the question whether a substance is to be placed under control or not. This is a political decision.’
Risk assessment guidelines

6 Recommendation

The Council Decision does not request the Scientific Committee to include a recommendation in their report. However, based on the experience thus far, it is clear that it is good risk assessment practice to do so. The Council has to decide whether to submit the new psychoactive substance to control measures (Art. 8.3). Therefore a recommendation should include a science-based advice to this end. A recommendation should indicate whether a new psychoactive substance is considered a narcotic drug similar to those in the Schedules annexed to the 1961 UN Convention or a psychotropic substance similar to those in the Schedules annexed to the 1971 UN Convention. In addition as far as can be judged from the available data it should be indicated which of the Schedules under the UN Conventions contains substances most similar to the new psychoactive substance. If the new psychoactive substance is not similar to those listed in the Schedules annexed to the UN Conventions, but the Scientific Committee would still conclude that it is recommendable to submit the new psychoactive substance to measures of control, than the reasons for this recommendation should be further specified. If the Scientific Committee concludes that the new psychoactive substance should not be recommended to be submitted to control measures, the reasons for this recommendation should also be specified. Further recommendations may include suggestions what alternative actions are considered sensible at the level of the Union or the Member States.
6 Conclusion
The Council Decision does not explicitly request the Scientific Committee to include a recommendation in their report. However, based on the experience thus far, it is clear that it is good risk assessment practice to provide a science-based opinion. Following an initiative of the Commission, the Council has to decide whether to submit the new psychoactive Substance to control measures (Art. 8). The opinion should therefore indicate whether a new psychoactive substance could be considered a narcotic drug similar to those in the Schedules annexed to the 1961 UN Convention or a psychotropic substance similar to those in the Schedules annexed to the 1971 UN Convention. In addition as far as can be judged from the available data it could be indicated which of the Schedules under the UN Conventions contains substances most similar to the new psychoactive substance. If the new psychoactive substance is not similar to those listed in the Schedules annexed to the UN Conventions, but the Scientific Committee still provides an opinion that tends towards submitting the new psychoactive substance to measures of control, than the reasons for this opinion should be further specified. If the Scientific Committee concludes that the new psychoactive substance does not require control measures, the reasons for this opinion should also be specified. Furthermore, the opinion may include suggestions what alternative actions are considered appropriate at the level of the Union or the Member States.
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