



Analogue controls: An imperfect law

Dr L. A. King

Professor D. Nutt, Imperial College London

N. Singleton, UK Drug Policy Commission

R. Howard, UK Drug Policy Commission

Introduction

The challenge posed to established drug control measures by new psychoactive substances, so-called 'legal highs', that are emerging with increasing rapidity and being distributed through new channels, such as the internet, has become the focus of increasing attention in the United Kingdom.¹ In response to this increasing concern, in late 2011, the Advisory Council on the Misuse of Drugs produced a report examining these novel substances. One of its recommendations was that the government should "explore the possibility of new legislation similar to the Analogue Act (1986) used in the USA and similar laws in other countries, in conjunction with generic definitions of chemical scope" (Advisory Council on the Misuse of Drugs, 2011, p44).

Superficially the proposal seems attractive, especially for politicians who have come under intense media and public pressure to do something to prevent such substances becoming widely available. However, the experience of drug controls in general and analogue controls in particular raise serious doubts about the efficacy of adopting analogue controls in the UK as suggested by ACMD.

In this joint Briefing Note, the Independent Scientific Committee on Drugs and the UK Drug Policy Commission set out some of the drawbacks with analogue control systems.

Context

In the past twenty years, the problem of novel substances in Europe has steadily risen up the political and public agenda. The modern era can be traced directly to the publication of PIHKAL (Shulgin and Shulgin, 1991), a book that provided detailed recipes for the synthesis of over 170 substances broadly related to MDMA. By 1997, the European Union (EU) had set up a 'Joint

¹ For example, the 2010 Drug Strategy in the UK incorporates specific mention of the issue (HM Government, 2010).

Action' to monitor 'New Synthetic Drugs', and to provide for their risk assessment and EU-wide control in appropriate cases. This was succeeded by a EU Council Decision of 2005 (European Commission, 2005) that widened the scope to what are now formally known as 'New Psychoactive Substances'. These new substances have appeared at an increasing rate. In 2011, forty-nine were notified to EMCDDA, and over 200 have been recorded since 1997 (EMCDDA, 2012).

The sheer volume of these new substances and the speed with which they appear calls in to question the ability of the traditional approaches to drug control to keep pace and the costs involved are hard to sustain in a period of financial austerity. It is against this backdrop that approaches such as analogue or generic controls may appear appealing as shortcuts or cheaper options.

Analogue Controls in the United States

In 1986, the United States Congress passed the Controlled Substances Analogue Enforcement Act, commonly shortened to the 'Analogue Act'. This legislation arose as a response to the proliferation of numerous synthetic 'designer drugs' including narcotic painkillers, such as fentanyl derivatives, and phenethylamines related to MDMA (ecstasy) and amphetamine in the early 1980's. There seems little doubt that the Analogue Act was initially successful, at least in terms of its primary aim: many producers of designer drugs were prosecuted, and it seems that within a few years the designer drug problem in the United States (US) had largely disappeared.

The original 1986 Federal Analogue Act defined an analogue as a substance which is 'substantially similar' to a scheduled substance and has either an effect 'similar to or greater than' a controlled substance or is thought to have such an effect. However, the law did not define what 'substantially similar' means, nor did it try to clarify what would constitute a 'similar or greater' effect.

In response to a simple question about whether a chemical or drug is an analogue, there are some complex answers. In everyday terminology, the term 'analogue' is often used to describe a substance which has major chemical structures in common with another chemical. To organic chemists however the term 'analogue' has a more precise meaning. It is also the case that many chemicals that look alike and have similar chemical structures react very differently both in and out of the body. So the issue is not at all clear-cut.

The essential principle of analogue control is that it requires a judgement to be made on whether, (i) a suspect substance is substantially similar in its chemical structure to an existing controlled drug and, (ii) on whether that substance has a substantially similar stimulant, depressant or hallucinogenic effect to an existing controlled drug. Courts in the US have interpreted the law as meaning both (i) and (ii) must apply. The main appeal of the analogue concept is that it provides a means of avoiding a full risk assessment, particularly when little scientific information may be available on which to base such an assessment. In US cases, analogue control has been used on a substance-by-substance basis. In other words, no extrapolations can be made and each new substance requires a further hearing and judgement to be made.

The difference between analogue and generic control measures

Analogue control measures operate on a substance by substance basis. A substance that is both structurally similar and has a similar or greater effect on the central nervous system as an already controlled substance is deemed to be a controlled substance analogue and as such is also controlled.

Generic control measures relate to groups of substances. Starting from a core molecular structure, which does not itself have to be psychoactive, it specifies particular variations of the structure (particular substituent groups in specified positions in the molecule) which lead to a substance being controlled. Thus each substance does not have to be dealt with individually and new types of substances can be controlled through this approach.

Analogue control differs from generic control in being based on similarity to substances that are already controlled and deals with substances individually. The essence of a generic definition is that it focuses on broad groups of substances (see box). A few generic definitions in the Misuse of Drugs were added at its inception in 1971.² Others, such as ecgonine derivatives and pentavalent derivatives of morphine date back to the United Nations 1961 Convention. However, most generic definitions in the Act have been introduced since 1977 (King, 2009). They now cover the following groups: anabolic steroids, barbiturates, cathinones, fentanyls, pethidines, phenethylamines, phenyl- and benzylpiperazines, synthetic cannabinoid agonists (cannabimimetics) and tryptamines. In 2012, it is planned that pipradrol derivatives will join this long list. A common feature of generic definitions (and a disadvantage to a lay reader of the legislation) is that, in most cases, no individual controlled substance is mentioned explicitly. Thus, for example, one will search in vain in the Misuse of Drugs Act for "MDMA" or "mephedrone" or any of their chemical synonyms. A further disadvantage of generic control is that the definitions may be unintelligible to all but organic chemists.

Recent developments in the United States

By contrast to the European experience, and after that initial phase in the 1980's, the phenomenon of novel substances in the US has only resurfaced in the past few years. Some commentators have suggested that this long period of absence was a measure of the effectiveness of the Analogue Act. But closer inspection of the evidence does not support this. For example:

- Almost all of the case law that built up around the Act is quite old.
- The US Drug Enforcement Administration (DEA) now considers the Analogue Act an "Imperfect Law", and has recommended that the UK should not adopt a similar approach (Wong et al., 2010).
- The US Congress (US Congress, 2011) has proposed that the two most conspicuous groups of new substances (cathinone derivatives and cannabinoid agonists) should be

² They include *N*-alkyl derivatives of lysergamide (substances closely related to lysergide [LSD]) and cannabinols (including THC).

placed in Schedule I of the Controlled Substances Act without relying on the Analogue Act.

- Other countries (e.g. Canada, New Zealand, parts of Australia) adopted analogue controls in the 1980's, based on the US model, but the legislation was rarely used.
- There are no similar examples of analogue control in any European country.

Problems with analogue control

A comprehensive critique of the Analogue Act has been provided by Kau (2008). Together with experience from other sources, the main problems identified, several of which also apply to generic controls, were:

Constitutional acceptability

Whereas with explicit listing of substances in a schedule or even a generic definition, the status of a substance is clear from the outset, the use of analogue legislation requires that a court process should determine whether the substance is or is not controlled. It has been argued that such a retrospective process undermines the right of a defendant to know from the outset whether an offence has been committed. In the US, the Analogue Act was deemed not to be constitutionally vague (*United States v. Allen McKinney*, 1995), but a different view might be taken by European courts.

Determining what is meant by "substantially similar"

No US court has ever given guidelines on what is "not substantially similar". Experience shows that interpretation usually degenerates into a 'battle of experts'. This is unsurprising. The concept of 'substantially similar' may require some scientific knowledge, but the outcome is no more than informed opinion. We might as well ask, for example, if Roquefort cheese is substantially similar to Stilton cheese. There is no right or wrong answer since it depends on the criteria used (e.g. appearance, smell, taste, method of manufacture, etc.). A similar subjective list of criteria could be drawn up for chemical substances (e.g. molecular weight, carbon skeleton, functional groups, ease of conversion into the controlled substance, immediate precursor, probable effect on humans, etc.).

Permanence of decisions

Judgements about which analogue is deemed to be a controlled substance may not be binding on other courts. There is the related possibility that different courts might come to different conclusions about the same chemical entity.

Substances beyond control

Unique entities, which are unlike any controlled drug in terms of their chemical structure, are beyond the scope of analogue control. This problem exists also for generic control. Examples here are the active principals of *Salvia divinorum*, *Mitragyna speciosa* and a number of other plant-based psychoactive substances.

Determination of psychoactivity

In the absence of published scientific data - a common situation with novel substances - then if a substance is not sold overtly for human consumption any conclusion about stimulant, depressant or hallucinogenic effects must rely on anecdotal reports from users.

Impact on research

Analogue control could have a negative impact on legitimate pharmaceutical research. Although this might also occur with generic controls, in that situation it is at least possible to work out in advance (if you have sufficient expertise) if a new compound is covered by a generic definition. With analogue control no such surety exists and, in the face of uncertainty, limiting the use of whole groups of substances in research and thus avoiding the issue may seem the pragmatic alternative.

Conclusion

In their report on new psychoactive substances, the Advisory Council on the Misuse of Drugs (ACMD, 2011) considered analogue control in a positive light. Furthermore, the report proposed that some of the above problems could be resolved by having a statutory agency determine if a questioned substance was substantially similar to an existing controlled drug. However, in addition to the costs associated with such a body, this fails to address the arbitrary nature of any such decisions, and raises the prospect that those decisions could be liable to judicial challenge. Nor will the use of generic definitions of chemical scope overcome the requirement to demonstrate both structural similarity and similarity of effect on a case by case basis. We agree with the US Drug Enforcement Agency that their analogue legislation is no longer fit for purpose and hence it would be inappropriate to adopt the approach here.

We similarly caution against any excessive, informal use of the analogue principle. For example, methoxetamine is currently the subject of a Temporary Class Drug Order (Legislation.gov.uk, 2012). At the end of the one-year period there might be a temptation to suggest that it is sufficiently similar to ketamine (a Class C controlled drug) to warrant control for that reason alone, without specific evidence relating to methoxetamine itself. However, analogy with other substances should never be seen as more than a minor part of any formal risk assessment process since, as is discussed in more detail on the Appendix, substances with apparently similar structure may have completely different effects and hence risks from use.

While the fast pace of development of new psychoactive substances suggests a new approach to control is needed, analogue control is not likely to be effective. Such a measure is unlikely to have much impact on supply or use because it does not address the fundamental problems of enforcing controls on an increasingly broad, and rapidly changing, range of substances that are distinguishable only by detailed forensic analysis: an issue it shares with generic control measures.

As discussed in a recent report from UKDPC (Birdwell et al., 2011) there are many options for regulating new substances, but analogue control should not be one of them. There is also a clear need for more research into the pharmacology of new drugs to provide robust information to

underpin prevention, harm reduction and treatment measures that need to go alongside control measures.

Rather than seeking 'short-cuts' to the control of new substances through an analogue system, the ACMD, forensic and social science bodies should be appropriately funded to carry out thorough assessments of new substances to gauge their relative and actual harms and provide the information necessary to respond to these.

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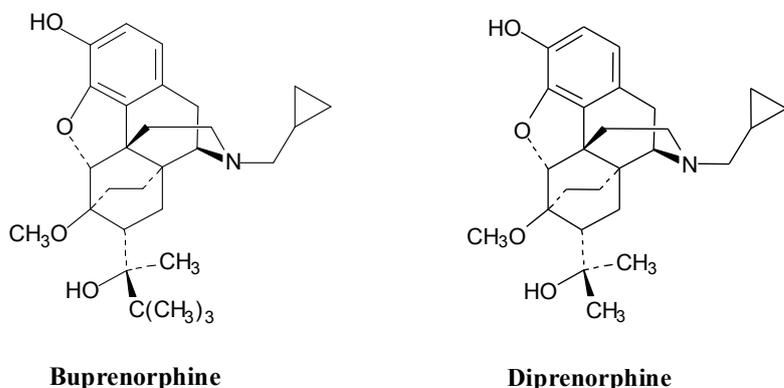
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Appendix: The problem with similarity

Both generic and analogue control approaches are essentially based on the proposition that substances with similar structures are likely to behave similarly within the human body. However, as stated earlier, while this can be true it is not necessarily the case. In some circumstances a very small change can simply make a substance inactive but in other cases very similar substances can have diametrically opposed action. For example, two of the active compounds in cannabis, tetrahydrocannabinol (THC) and cannabidiol, have similar structures but while THC produces the classic cannabis effects of being “stoned”, cannabidiol has no such effect and indeed may if anything block some of the psychic actions of THC itself as well as reducing anxiety. For these reasons cannabidiol is being studied as a possible treatment for some psychiatric conditions.

Two compounds, with even more similar structures (show below), are buprenorphine and diprenorphine. Buprenorphine is a moderately powerful opioid agonist (i.e. it binds to the opioid receptors in the brain) that is used as a treatment of heroin dependence and is itself sometimes abused. Diprenorphine is an opioid antagonist (which means it blocks the effect of opioids), so is not only not abused but is a very useful tool for brain imaging.

Figure: Two substances with very similar structures but very different actions



These examples demonstrate the way in which use of both analogue and generic control measures may not only lead to controls on substances that are not likely to be abused but also the potential for, in so doing, preventing the development of substances that may have medical or other benefits.