Drug analogues and substantial similarity, views of an expert witness

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Expert witnesses have an important role to play in assisting judges and juries to make informed decisions in court. They are to provide assistance to the decision makers, not to confuse them. Difficult legislation does not help to give clear and precise opinions. The author has appeared as an expert witness in a number of cases concerning chemicals that may be considered as illicit if they are considered to be analogues of and/or substantially similar to known banned chemicals as outlined in the Commonwealth Criminal Code. This is a personal view based on appearing as an expert witness for the Commonwealth Department of Public Prosecutions in court proceedings. The author also draws on his experience as a Specialist Member of the Administrative Appeals Tribunal considering evidence from expert witnesses. The key issues for this review are what is a ‘drug analogue’ and are two or more chemicals ‘substantially similar’ in structure?

Keywords: drug analogues; substantial similarity; Criminal Code; addition; Nexus; amphetamines; cathinones; experts

There has been a series of recent cases coming to the Commonwealth Department of Public Prosecutions (CDPP) regarding chemicals that may be considered as illicit if they are analogues of and/or substantially similar to known banned chemicals as detailed in the Commonwealth Criminal Code. The author has appeared in several of these cases as an expert witness for the CDPP. This review is based on an invited lecture on ‘Drug Analogues’ given to the CDPP National Conference on ‘Illegal Imports and Exports, and Human Exploitation and Border Protection’ in Canberra in 2015. The author also draws on his experience as a Specialist Member of the Administrative Appeals Tribunal considering evidence from expert witnesses. The key issues for this review are what is a ‘drug analogue’ and are two or more chemicals ‘substantially similar’ in structure?

The author’s fields of expertise are medicinal chemistry, organic chemistry and pharmacology, specialising in investigating analogues of chemicals that act on the central nervous system. He has more than 400 peer-reviewed publications in this general area. In addition, he has substantial experience at the science-law interface as a Specialist Member of the Commonwealth Administrative Appeals Tribunal (AAT) 1991–2014. His AAT cases generally involved administrative decisions on a wide range of chemicals, from pharmaceutical chemicals and herbal products to agricultural, industrial and veterinary chemicals, sitting as part of a two- or three-member tribunal in which at least

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one member was legally qualified. From the Tribunal bench he has taken evidence from and examined many expert witnesses.

**What is an analogue?**

The *Oxford Dictionary* defines the noun *analogue* as ‘a person or thing seen as comparable to another’. It refers to its use in Chemistry as ‘A compound with a molecular structure closely similar to that of another’.

The *Macquarie Dictionary* describes the chemical usage of the noun *analogue* as including ‘an organic compound that has a similar structure to another compound’.

**Chemical analogues**

The scientific description of a group of chemicals as analogues is based on similarities in chemical structure. It does not mean that the chemicals are readily synthesised from one another, although a group of chemicals may be prepared from a common starting chemical. The starting chemical is often referred to as a precursor chemical.

Despite their structural similarity, chemical analogues can have different chemical, pharmacological or toxicological properties.

Medicinal chemists make analogues of a chemical of interest or a lead chemical in order to understand how the chemical may act on a drug target and to improve the potency and selectivity of that action. Chemical analogues may be made to get around patents. Analogues are obtained by chemical synthesis from suitable precursor chemicals or from commercially available collections of related chemicals. The analogues may have improved solubility properties over the original chemical, better pharmacokinetic properties or less toxicity.

The author has spent much of his research career investigating analogues of the chemical neurotransmitter GABA. He has 36 peer-reviewed publications that contain the word ‘analogue’ in the title. At the time of writing, his most recent publication in this field is titled ‘Unsaturated analogues of the neurotransmitter GABA: trans-4-aminocrotonic, cis-4-aminocrotonic and 4-aminotetrolic acids’\(^1\). This work describes the different pharmacological effects on these three analogues of GABA and how this led to this discovery of a new class of receptors for the neurotransmitter. The structural similarities of these analogues are clear to most trained chemists. These analogues, however, behave differently in their interactions with enzymes, receptors and transporters that interact with GABA. The point of making them was to obtain chemicals that were structurally similar to GABA that had more selective actions than GABA itself due to unsaturated chemical bonds restricting the shape on the analogue compared with GABA. Different shapes of GABA, a very flexible molecule, are considered to interact with different enzymes, receptors and transporters.

**Drug analogues**

The scientific and general literature contains numerous reports of the development of analogues of illegal drugs to circumvent laws and regulations.

These analogues are sometimes called designer drugs.

Using the chemical database SciFinder\(^2\), based on the American Chemical Society’s Chemical Abstracts and other chemical databases, it is relatively easy to search for peer-reviewed publications that contain the name of a potentially illegal drug described...
by the authors as an analogue of an illegal drug in the title or abstract of the publication.

For example, the description of the potential illegal drug MPPP (4-methyl-alpha-pyrrolidinopentiophenone), the illegal drug Methcathinone, and related substances of the amphetamine group as analogues of one another is well established in the scientific literature. MPPP is described as a second generation cathinone. It is described as a Methcathinone analogue in Saha et al. and in Chawla et al.

Such descriptions of analogues are by medicinal chemists and pharmacologists writing about their research studies. While conforming to widely accepted chemical norms, these are not necessarily based on legal definitions. Legislative authorities have sought to legally define such analogues on the basis of defined structural similarities to illegal drugs in order to describe what may be considered to constitute a drug analogue in a legal sense.

**Use of the term drug analogue in law**


In this act, the term ‘controlled substance analogue’ is defined as a substance ‘the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II’. The term *substantially similar* has become an important concept in such legislation.

**McEwen – Nexus**

In 1997–1998, the author was an expert witness in the New South Wales District Court that was subsequently appealed to the Supreme Court of New South Wales Court of Criminal Appeal in a case generality referred to as ‘McEwen’. The chemical and pharmacological issues in this case concerned whether a chemical described as Nexus was a substance ‘structurally derived from methoxyphenylethylamine’ (Figure 1) and had hallucinogenic properties.

Crown expert witnesses gave evidence that Nexus was such a substance while the defence witnesses said it wasn’t. The defence witness included Alexander Shulgin who was famous for his classic book *Pikhal: A Chemical Love Story*, at that time banned in Australia, and being the first person to make Nexus and describe its effects on humans.

The case involved multiple defendants and thus multiple counsel – and was conducted in an aggressive adversarial manner. Coming from the AAT and its inquisitorial

![Chemical structures of Nexus and 2-methoxyphenylethylamine.](Figure 1)
but temperate proceedings, the author found this difficult. The Crown won the case and the expert evidence was commented on favourably by the appeal judge.

The appeal judgment stated that words ‘structurally derived’ in the clause ‘and other substances structurally derived from methoxyphenylethylamine’ needed expert evidence in explanation. It states that:

Without that evidence a court would not have understood the issues which arose. The evidence adduced explained the field of discourse in which the phrase ‘structurally derived’ was used. The word ‘derived’ was explained as was the phrase ‘structurally derived.’ The evidence had the effect of pointing up the meaning of that word and that phrase in the Schedule to the Statute. The evidence given would not have confused the jury – instead it would have helped them understand and undertake their task.

The structures of the key substances, Nexus (4-bromo-2,5-dimethoxy-phenylethylamine) and 2-methoxyphenylethylamine, a scheduled chemical, are shown below to illustrate how Nexus is structurally derived from the scheduled chemical.

Nexus was subsequently added to the list of scheduled chemicals. Importantly in the judgment, evidence was also accepted that ‘structurally derived’ does not involve the ability to convert one substance into the other.

Commonwealth Criminal Code

In 2014, the author retired from the Commonwealth Administrative Appeals Tribunal and early in 2015 was contacted by the Commonwealth Department of Public Prosecutions regarding acting as an expert witness in a number of cases on drug analogues under the Commonwealth Criminal Code. After some reluctance given his earlier experience with criminal proceedings, he agreed to provide expert witness statements on a number of chemicals being considered in various proceedings. This led to court appearances in Gosford, Melbourne, Adelaide and Darwin. The issues of interest were detailed aspects of the Commonwealth Criminal Code, s.314.4 pertaining to ‘drug analogues’.

Sub-section (2) of s.314.4 provides that a substance (referred to as a ‘drug analogue’) is also a border controlled drug if it is related to one of the listed substances in one of a number of specified ways. In 2013 the legislation was as follows:

A substance is also a border controlled drug if the substance (the drug analogue) is, in relation to a border controlled drug listed in subsection (1) (or a stereoisomer, a structural isomer (with the same constituent groups) or an alkaloid of such a border controlled drug):

a) a stereoisomer; or
b) a structural isomer having the same constituent groups; or
c) an alkaloid; or
d) a structural modification obtained by the addition of one or more of the following groups:
   i. alkoxy, cyclic diether, acyl, acyloxy, mono-amino or dialkylamino groups with up to 6 carbon atoms in any alkyl residue;
   ii. alkyl, alkenyl or alkynyl groups with up to 6 carbon atoms in the group, where the group is attached to oxygen (for example, an ester or an ether group), nitrogen, sulphur or carbon;
   iii. halogen, hydroxy, nitro or amino groups; or
e) a structural modification obtained in one or more of the following ways:
i. by the replacement of up to 2 carbocyclic or heterocyclic ring structures with
different carbocyclic or heterocyclic ring structures;
ii. by the addition of hydrogen atoms to one or more unsaturated bonds;
iii. by the replacement of one or more of the groups specified in paragraph (d)
with another such group or groups;
iv. by the conversion of a carboxyl or an ester group into an amide group; or
f) otherwise a homologue, analogue, chemical derivative or substance substantially
similar in chemical structure;
i. however obtained, except where the drug analogue is separately listed in sub-
section (1).

The issues that involved most arguments were ‘(d) a structural modification
obtained by the addition of one or more of the following groups’ and ‘(f) otherwise a
homologue, analogue, chemical derivative or substance substantially similar in chemical
structure’. These will be referred to as the ‘Addition’ and ‘Substantially similar’ issues.

Addition as used in the Criminal Code

The general meaning of the noun *addition* in the *Oxford English Dictionary* is ‘Some-
thing which is added or joined to another thing; an appendix, an augmentation; wing, room, etc., added as an extension of an existing building.’

Similarly, in the *Macquarie Dictionary*, *addition* is the ‘the act or process of adding
or uniting’.

In strict chemical usage, ‘addition’ has a more specific meaning – *Oxford English
Dictionary*: ‘The combination of one molecule with another to form a larger molecule
with no other products’; *Macquarie Dictionary*: ‘addition compound noun a compound
formed by chemical addition, with no secondary products’. This is addition in the arith-
metic sense.

While superficially it is tempting to give ‘addition’ its strict chemical meaning in
section 314.4(2) of the Criminal Code, more detailed consideration indicates that here
‘addition’ is used in the general sense.

Of the structural modifications specified in section 314.4(2)(d), very few of those
listed could be obtained in fact by an addition of one of the groups listed in the chemi-
cal sense where the final product contains the same number of atoms as the total num-
ber in the molecules from which it is formed, with the possible exception of a cyclic
diether. In general, hydrogen atoms are ‘lost’ in such an ‘addition’.

Certainly, medicinal chemists routinely talk of the ‘addition’, for example a methyl
group to a chemical in order to produce a more desirable substance. In such cases there
is usually the loss of a hydrogen atom from the starting chemical in producing the
product. Thus, medicinal chemists routinely use the term ‘addition’ in the general
sense, i.e. as in an ‘addition’ to a house whereby something is lost from the original
house in making the addition.

If ‘addition’ were to be read only in the very narrow chemical sense, addition of all
but a very few of the structural modifications listed in sub-paragraphs (i)–(iii) would be
essentially impossible. It follows that for section 314.4(2)(d) to be meaningful,
‘addition’ must be read in its widely used general sense.
Recent judgments in cases where the author has appeared as an expert witness support this.

**Woods J, in 2013/00108032 - R(Commonwealth) v Daniel Archer BARBER**

When the Crown addressed the Court it was submitted that the word ‘addition’ in subs (2) is not limited to simple addition in the formal chemistry sense, but it is used in a broad sense. As if, for example, one imagines a house extension being undertaken, so that if a new room is to be added, it may be also practically necessary to take away a window or some other part of the wall to which the new room was being added.

Using that analogy (which it seems to me is helpful) the contrary argument by the defence was that there cannot be ‘addition’, as it were by analogy with house extension, because the formal language of the statute incorporates or is based upon the language of chemistry – and in the formal language of chemistry it must be as if the house extension were made without any alteration, removal or detraction from the house.

I note that both the distinguished professors who have given evidence here, accept that working chemists do sometimes use the language of chemistry in a colloquial sense, or as shorthand. In my view that is the way that one should approach the interpretation of the word ‘addition’, for the legal purposes here.

**Slattery J, in 2015/SADC 127 – R v Thomas and Bergin**

The legal meaning of a border controlled drug for s.314.4(2)(ii) of the Code turns on the meaning of the ‘addition’ and that term is to be constructed broadly.

I accept the evidence of Professor Johnston that if the word ‘addition’ was to be read as meaning ‘addition reaction’ then the content of s.314.4(d)(i)(ii)(iii) would be rendered nugatory because those words be otiose and no meaning would be given to them, This is contrary to the basic tenets of statutory construction.

The phrase ‘addition reaction’ has not been used by Parliament in the sub-section. Parliament has chosen to the use the word ‘addition’ in the statute. This is a broader form of expression. This approach was favoured by the Courts of Appeal of New South Wales and Tasmania in their decisions in McEwan and Daley respectively.

**Southwood J, in The Supreme Court of the Northern Territory, 2015, SCC 21348065 R v Collocot**

The evidence of the Crown expert, Professor Graham Johnston, was that alpha-PvP is an analogue of methcathinone and shares a substantial structural similarity with methcathinone. His expert opinion was also that alpha-PvP is a substance which in relation to methcathinone is a structural modification obtained by the addition of two alcohol groups, one with two carbon atoms, the other with three carbon atoms. A diagram was tendered in evidence showing those similarities and structural changes. This evidence was unchallenged at the trial and established beyond a reasonable doubt that alpha-PvP is a border controlled drug that is within the extended definition of a border controlled drug which was contained in s 314.1(2)(d)(ii) and (f) of the Commonwealth Criminal Code at the time of this offending.
In referring to the ‘addition’ problem in the Criminal Code, Hibbert and Sutton\(^{10}\) has suggested the subsection should read: ‘a structural modification obtained by the substitution of one or more hydrogen atoms by one or more of the following groups’. This would solve the immediate ‘addition’ problem in the Code.

**Substantially similar as used in the Criminal Code**

There is a rich literature of the use of the term ‘substantially similar’ in copyright law. Under copyright law, substantial similarity refers to a strong resemblance between a copyrighted work and an alleged infringement. Thereby, it creates an inference of unauthorised copying. The standard for substantial similarity is whether an ordinary person would conclude that the alleged infringement has appropriated non-trivial amounts of the copyrighted work’s expression. This standard is not rigorously defined and is somewhat subjective. Although at the heart of copyright law, the area of substantial similarity remains one of its most elusive aspects.

In the academic world we can readily assess written work such as student assignments for plagiarism using computer programmes such as Turnitin\(^{11}\). Such programmes provide a percentage figure for the degree of similarity between two written works. What actually constitutes plagiarism depends on informed but subjective assessment that varies from case to case and in serious cases is usually subject to appeal.

The standard for substantially similar with chemical substances as used in the Criminal Code is even less well defined. In an article entitled ‘Analogue controls: an imperfect law’ King et al.\(^{2}\) write:

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.).

The author’s opinion is that two substances are similar if half of the non-hydrogen atoms are in approximately the same three-dimensional space. They are substantially similar if two thirds of the non-hydrogen atoms are in approximately the same space.

This allows for two thirds on the non-hydrogen atoms in two substances to interact with the sites on enzymes, receptors and transporters in the same way, with the other third of the non-hydrogen atoms contributing some diversity. Thus, while the substances would be ‘substantially similar’ they would nonetheless be different in their detailed interactions. This diversity is why analogues are made. The two-thirds condition is admittedly somewhat arbitrary but is not unreasonable given what can be gleaned from copyright law.

Space in this context is three-dimension space. Where a series of chemicals are relatively flat, as for example in the case of amphetamines, it is convenient to draw them on paper as two-dimensional structures, as in this article. Many chemists can evaluate two-dimensional structures readily in three-dimensions, indeed they are considered to think in three-dimensions. Computer modelling in three-dimensions is of course available and indeed necessary for assessing more complex molecules.
There have been many attempts to quantify chemical similarity with varying
degrees of success. One example is the use of the Tanimoto coefficient that can be
accessed through the Royal Society of Chemistry’s ChemSpider facility (www.chemspi
der.com)\textsuperscript{13}. As noted by Hibbert and Sutton\textsuperscript{10} it is not suited to comparisons of low
molecular weight substances where the similarities are obvious but underestimated by
the Tanimoto coefficient.

**Analogues of Methcathinone**

This figure (Figure 2) from Shanks et al.\textsuperscript{14} shows 13 substances derived from the
prohibited drug Methcathinone by structural modification as indicated. Is it beyond

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**Figure 2.** Structures of compounds related to Methcathinone from Shanks et al.\textsuperscript{14} with permission.
reasonable doubt that some or all of these substances are analogues and/or substantially similar?

Shanks et al. consider the 13 substances are indeed analogue of Methcathinone but are they sufficiently similar in structure to be considered as ‘substantially similar’ beyond reasonable doubt? Expert evidence needs to be before a court in a form that is understood by a judge and/or jury unskilled in the art of chemistry. Diagrams such as this are a great help.

Of the 249 chemicals listed as controlled drugs in the 2015 Criminal Code, 37 are derivatives of Methcathinone. Of the 14 chemicals listed in Shanks et al., only two are not listed as prohibited substances in the code. These are 4-EMC and Pentedrone and they are covered by section 314.4(2) as they represent simply the addition of an ethyl group to Methcathinone. The author considers that all 14 chemicals are substantially similar beyond reasonable doubt.

Expert witnesses

In McEwan the evidence of expert witnesses was vital. The appeal judge on reviewing the evidence stated: ‘Without that evidence a court would not have understood the issues which arose’ and further ‘The evidence given would not have confused the jury – instead it would have helped them understand and undertake their task’. That is the real task of expert witnesses – helping the judge and jury understand the issue, and not to confuse them.

Judge Garry Downes, as then President of the Administrative Appeals Tribunal and a Judge of the Federal Court of Australia has stated that ‘There has been a perception that expert evidence takes up too much time and that experts have a tendency to be partial.’ His experience is based on examining expert witnesses during his long career as a barrister and on hearing their testimony in the AAT: both sides of the bench, as it were. He writes of expert witnesses that:

with very few exceptions, they do not deliberately mould their evidence to suit the case of the party retaining them. When they do, this emerges. They certainly expose the matters which support the hypothesis which most favours the party calling them. But, provided the matters are legitimate and that any doubt as to the strength of the hypothesis is exposed, I see nothing wrong with this. Indeed, I think this process is one of the great values of the traditional approach to expert evidence. It is exposing different expert points of view for evaluation by the judge.

The author’s experience as a Specialist Member of the AAT, who sat with Judge Downes on several key cases, supports this view of expert evidence. Such evidence does take up a lot of time (but not as much as procedural fairness issues) and efforts are being made to address this. Concurrent evidence is used extensively in the AAT and by various courts. Usually this involves two or more expert witnesses together in the witness box being examined by barristers from both sides. In the author’s experience it is desirable that the expert witnesses are allowed to ask each other questions. This works in an inquisitorial system such as the AAT but is more problematic in an adversarial court where the barristers like to control their case.

The author had a recent experience of concurrent evidence in Gosford in the case of R v Barber where he sat in a very cramped witness box with Professor Hibbert who gave evidence for the defence. Fortunately the witnesses knew each other very well and agreed on many substantive points, as usually happens with concurrent evidence but they differed on whether two chemicals were substantially similar, with
Professor Hibbert maintaining that there was reasonable doubt and the author that there was none. In his judgement the judge wrote:

I want to refer to aspects of the evidence by the two professors who were presented literally together in the witness box in the procedure adopted in modern times which is sometimes referred to as ‘hot tubbing’. This is a very useful mode of taking expert evidence.

Both witnesses were questioned carefully by the Crown and by the defence.

The author has no doubt that the taking of expert evidence is improving. The use of court-appointed expert witnesses is worth exploring further. On the AAT, Specialist Members provide expert independent judgment on issues within their expertise, e.g. medical or tax issues, or – in the case of the author – chemical issues. This works well. But they are not witnesses who can be cross examined. Their findings are detailed in the decisions that do address specific issues raised by the expert witnesses. AAT decisions are based on the balance of probabilities, whereas in the criminal court decisions are based on beyond reasonable doubt. While the AAT is the final determiner of fact, AAT decisions are appealable to the Federal Court on the basis of law.

To sum up, expert witnesses are to provide assistance to the decision makers, not to confuse them. Difficult legislation does not help to give clear and precise expert opinions. The drug analogue section of the Criminal Code is such difficult legislation.

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