References

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How Similar Is Substantially Similar?

> "When *I* use a word," Humpty Dumpty said, in rather a scornful tone, "it means just what I choose it to mean—neither more nor less."
> "The question is," said Alice, "whether you *can* make words mean so many different things."
> "The question is," said Humpty Dumpty, "which is to be master—that's all."
>
> *Through The Looking Glass*
> Lewis Carroll, Macmillan, 1871

Sir:

In October 1986, the 99th Congress passed, and President Reagan signed, legislation called the "Anti-Drug Abuse Act of 1986." One of the several sections of this Act is known as the "Controlled Substances Analogue Enforcement Act of 1986." Many states, including California, enacted legislation that essentially mimicked the wording of this Federal Law. What it does is to make the laws and regulations that are in place for controlling illegal acts with scheduled drug equally applicable to unscheduled drugs, if these latter can be viewed as analogues. And to the extent that an analogue is intended for human consumption, it shall be treated as a Schedule I drug.

What is an analogue?

In the broadest usage, in the letters and arts, something is an analogue of something else if it is similar to it in function but different in structure or origin. The parent stem, analogy, was a Greek word that quite simply signified an agreement or correspondence between things that were in other respects different. And analogy can imply that if two things are alike in one way, they may be in another. In zoology, the wing of a bird and a butterfly wing are analogues. In linguistics, a potato and an apple are probably analogues in German (Kartoffel) and French (pomme de terre) but not in English or Italian. In mathematics, analogy was originally the basis of comparing ratios, but in current usage, analogue is contrasted to digital as a representation of continuous function.

In the area of chemistry and chemical structure, the use of the term has ranged from the most narrow sense to the most broad. The primary question that is being asked is, how can we compare the structures of two molecules? Are they both long and spindly, or short and squat, or planar or lumpy, or big and heavy, or small and light? Do they both have rings and/or chains and/or bumps or valleys or do they share similar weird atoms? The comparison of molecules very much depends upon which particular lens you are using for viewing.

In the narrowest of all interpretations, two compounds are analogues only if they differ by the replacement of one atom with another above or below it in the periodic table. The sulfur analogues of ethers. The silicon analogues of hydrocarbons. The next level of broadening comes from a horizontal license with the periodic table. The replacement of a carbon with an oxygen or a nitrogen, for example.

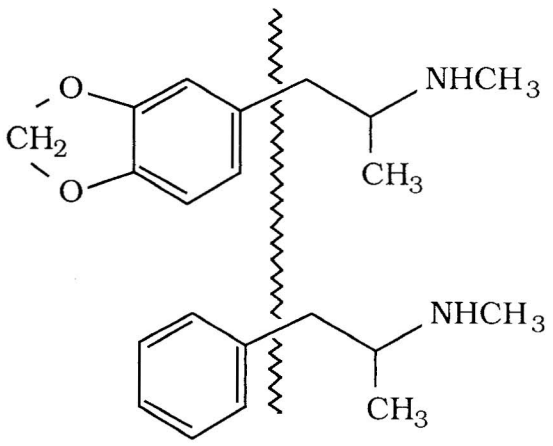
Yet looser rules can apply when an entire unit of a chain of units can be replaced with another. The analogues of a polypeptide may have a different amino acids at the valine position. Polysaccharide analogues might have new sugars at the terminal galactose position. And there are nucleic acids and synthetic polymers. Sometimes one group can be replaced with another to create an analogue, such as halo groups for alkyl groups.

And in the broadest examples, even the lengthening of a chain (theoretically, a homologue) or the rearrangement of atoms (theoretically, an isomer) have been structural changes referred to as analogues. Pick up a random copy of the *Journal of Medicinal Chemistry*. A sizable percentage of all titles incorporate the word "analogue" and all of the above usages are represented.

What applies to chemical structure applies equally to pharmacological function. Two drugs may be compared in an unlimited number of ways, comparing activity from the gross (they were both lethal) to the subtle (they showed similar receptor site kinetics). If the observer chooses one particular response and two drugs show it, he may well say that they are pharmacologically analogous. They become analogues. Another observer, looking for something else, may find them different from one another, and to him they are not analogues.

But all this is legally moot, since the term "analogue" has been explicitly defined in the 1986 law. A chemical is an analogue if its structure is "substantially similar" to that of a Schedule I or II drug. Or it is an analogue if it has a stimulant, depressant, or hallucinogenic activity that is "substantially similar" to that of a Schedule I or II drug. In short, the definition that is to be used in the enforcement of law has built into it a carefully worded vagueness. Nowhere are the terms "substantially" or "similar" defined. In everyday usage, the term "similar" means having something in common, that there is a close resemblance. The word "substantial" implies having substance, rather than being imaginary. Or being major (or strong, or heavy, or serious) rather than being minor (or weak, or light, or trivial). It is linguistically understandable to say that two structures are similar or that they are substantially identical. Either term means that they "kinda look alike." This calls for some subjective input by the speaker, but if his way of looking at two chemical structures (or two pharmacological responses) shows them to be somewhat alike, he can certainly call them "similar."

But the term "substantially similar" is hopelessly vague. I believe that it was crafted with this very goal in mind. By designing the net which has a completely variable mesh size, one can catch whatever fish one wishes to and let escape another fish that is not wanted. There is no objective standard to the term "similar" and certainly none for the phrase "substantially similar."



MDMA

Methamphetamine

Let me offer one specific example. I was asked a question by a lawyer a few weeks ago, in regard to the invocation of the California Analogue Bill. The charge was directed at the possession of MDMA, and it was based on the assumption that it had a structure "substantially similar" to that of methamphetamine. Methamphetamine, in California, is a Schedule II drug, and MDMA is not Scheduled. Above are shown the two structures being compared. The question that I was asked, "Do I think that these structures are "substantially similar?"

I have drawn a wiggly line to separate the aliphatic from the aromatic portion of these structures.

To the right of this line, there is found the same carbon chain, the same hetero-atom, the same number of atoms connected to one another in the same way, the same chiral center, and on and on. These halves are more than "substantially similar"; they are out-and-out identical.

To the left of the line, one finds two rings rather than one, two new hetero-atoms (the two oxygens), an additional carbon atom, three rather than five substitution positions on the benzene ring, and on and on. These halves are by no stretch of the imagination "substantially similar"; they are totally different.

In the eyes of a chemist who is attracted to aliphatic chains, these molecules might be analogues. And in the eyes of another chemist, one who thinks first in terms of rings and substitution patterns, these molecules are not analogues. The same ambiguity is obtained in the search for some "substantially similarity" between them in regard to their pharmacology. If one looks with an eye to heart rate and loss of appetite, they can be thought of as being similar. But with an eye to subjective effects and abuse patterns, they are totally dissimilar.

There is no "right" answer. There can never be one. And yet, charges are being brought and convictions are being obtained based on the "scientific" opinions presented in criminal cases. Eventually, a challenge to this preposterous wording will be made that will result in its removal from the law statutes. But until then, I fear that it will be imposed by the law enforcement groups when desirable, and ignored at other times. Any law that allows selective enforcement is bad law.

Alexander T. Shulgin, Ph.D.
1483 Shulgin Road
Lafayette, CA 94549

"Observations and Statistics Relating to Suicide Weapons": An Update

Dear Sir:

In a previous publication [*1*] data were presented for 202 weapons used in suicidal death. The experimental procedure has been continued and being presented herewith are data for a total of 650 cases.

As before, each of these cases has been ruled as a suicidal death by the Office of the Medical Examiner. Note also that each of the 650 cases is either a contact or loose contact wound.

These data are for weapons received in suicide cases from June 1985 to October 1988. Of the 650 cases, the distribution of weapon type is 54% revolvers, 20% pistols, 15% shotguns, and 11% rifles. In Table 1 the detection of blood inside and on the muzzle end of the various weapon types is given. Note that weapons submitted which had obviously been laying in a pool of blood were excluded from the study.

In Tables 2 and 3 the results of testing as broken down by caliber and weapon type for revolvers and pistols are given. In Table 4 the location of entrance wound sites by sex of decedent is shown.