

LOW REGULATORY CONCERN CHEMICALS (LRCC)

Discussion Paper No. 4

MODULAR ASSESSMENT OF CHEMICALS FOR WHICH APPROPRIATE ANALOGUES HAVE BEEN PREVIOUSLY ASSESSED BY NICNAS

1. PURPOSE

This discussion paper proposes a strategy for implementing the modular assessment of chemicals for which appropriate analogues have been previously assessed by NICNAS; through the development of regulations, criteria, guidance documents and other administration processes.

2. BACKGROUND

Recommendation 2.1 of the LRCC Final Report recommends that:

NICNAS introduce modular assessment fees for low hazard and or low risk chemicals and targeted assessment for chemicals where controls are in place such as:

Item C

- *Analogue chemicals.*

The modular assessment criteria presented here are for Item C; i.e. the modular assessment of new industrial chemicals notified under the certificate category for which an appropriate analogue has been previously assessed by NICNAS.

2.1 Current Situation

In Australia, new chemicals require a full notification package regardless of their similarity or analogy to other chemicals previously assessed by NICNAS.

In many cases, such analogue chemicals represent no greater risk to human health and the environment than an analogue already assessed by NICNAS or another local or international regulatory authority. However, manufacturers or importers are required to submit similar notification packages with similar fees to those required for a new chemical notification. As well as the assessment periods and the financial costs involved for analogues, there are also potential issues such as additional animal testing and use of regulatory resources that could be better utilised.

There currently exists no mechanism to fast track the assessment of analogue chemicals via reduced testing requirements, even though, both in Australia, and overseas, a notification may often rely on analogue data for determination of their toxicological and environmental endpoints. Other countries such as New Zealand and the US make allowance for chemical analogy in the assessment of new chemicals and in some circumstances provide a specific notification pathway for such chemicals.

3. CRITERIA FOR ACCEPTABLE ANALOGUES

Where it can be demonstrated that a notified chemical has a similar structure and pattern of activity to an (analogous) chemical already assessed by NICNAS, it is possible to fast track the assessment process without compromising human health and the environment.

3.1 Analogue defined

While an analogue¹ can be simply defined as a chemical compound that differs slightly in structure and properties from another compound², it is important to recognise that this permits variation to range from nil to slight, and limits must be determined. In the strict chemical sense analogues will be similar to each other, and in some cases may be equivalent (where the same capacity to combine or react chemically is required³), though rarely identical.

Under chemical patent law, an analogue can be defined as a compound similar in structure and function to another, previously described, compound to the point of "obviousness"⁴, whereupon, despite differing in some slight structural detail, it is no longer possible to grant an exclusive license on behalf of the former compound without infringing the rights previously granted to the latter.

In practice the recognition that one compound is structurally and functionally (spectrum of activity) "obviously" similar to another for the purpose of establishing patentability entails one "normally skilled in the art", having the reasonable expectation that compounds similar in structure will have similar properties, being motivated to deduce that the synthesis of a particular compound will be opportune.

The test for "obviousness" will be determined by what "one normally skilled in the art" determines a particular compound to be opportune. Often for chemical patents, a general class of chemicals is defined, which are presumed to be analogous. However, it is possible that an opportune compound or compounds may be discovered that have properties otherwise unknown or not obvious, even if within the defined scope of the class of chemicals and their previously presumed analogues.

As inventiveness covers all practical arts of human endeavours, the new desirable properties of the chemicals could relate to physical or chemical properties, different metabolic function (especially in the case of pharmaceutical chemicals), or alleviate environmental concerns. The desirable properties may be derived from selecting a certain chain length of alkyl group; or selecting a particular geometric or optical isomer etc. If such differences are deemed not to be obvious it follows that a patent could be properly granted and that the chemicals for which the patent is granted are not analogous to what has been previously broadly defined. The complexity of defining analogues from a patent sense is contained in numerous examples of legal findings that establish various principles of chemical similarity. (Some of these are cited in the examples and guidelines).

From the point of view of human health and ecotoxicity, it is important to note that a chemical compound with a structure similar to that of another, differing only slightly

from it with respect to a certain component, may yet have a *different* action metabolically. Thus while optical and geometric isomers are very similar structurally, where it is known that one isomer has a different activity (indicated by a significant variation in a toxicological end-point) or physico-chemical behaviour (such as a dramatically different water-octanol partition coefficient) from the other, they cannot be regarded as suitable analogues, one for the other.

Therefore for a chemical compound to be considered an analogue for notification and assessment involving toxicological data requirements, it must bear both a *prima facie* case of obvious structural similarity *and* demonstrate similar pattern of activity to the previously assessed compound. The latter criteria can often be demonstrated through a satisfactory closeness for at least one key physico-chemical and aquatic toxicity parameter required for ecotoxicological assessment, and one key toxicological endpoint required for human health assessment⁵. It is to be expected that notifiers may often be in the position to submit full physico-chemical and toxicological data for one member of a group of chemical compounds, produced for the purpose of exploiting the most functionally efficacious structure from within the group, and indicative data for all of the other similar structures.

As there will always be a level of uncertainty associated with any chemical on which a complete suite of (eco)toxicological tests have not been performed, regardless of the amount of analogue data available, a conservative approach to assessment of analogue chemicals is necessary to minimise risks. Thus where new chemicals are of particular concern, for example, because of toxicity to different taxonomic groups, persistence, or significantly different use patterns which may increase environmental as well as public exposure, data for the notified chemical should be submitted rather than analogue data.

3.2 Criteria for determination of analogy

For a nominated chemical to be regarded by NICNAS as an analogue of a previously assessed chemical, the following criteria must be met:

- *prima facie* structurally identical or similar (see below for criteria and guidelines);
- acute oral toxicity within 0.3 order of magnitude (+/-2x);
- aquatic toxicity within 0.3 order of magnitude (+/-2x) (for standard notifications) by data or argument as appropriate;
- n-octanol-water partition coefficient within 0.3 order of magnitude (alternatively; for polymers water solubility within 0.3 order of magnitude)⁶; and
- not the subject of a hazard assessment or otherwise of concern.

3.3 Criteria for determination of structural identity

The following cases are examples of potential structural identity with expected similar reactivity profiles for toxic effects (if any):

3.3.1 Chemical identity *in vivo*

An analogue is identical *in vivo* to the previously notified chemical:

- where the Na⁺, K⁺ or NH₄⁺ salt of the acid is present in solution;
- where the Cl⁻, CO₃²⁻, PO₄³⁻ or SO₄²⁻ salt is present in solution;
- where it is related through some precursor, metabolite or breakdown product *in vivo*.

3.3.2 Polymer identity

Where a polymer is manufactured by a different pathway (i.e. by using different reactants) and chemically identical, though the resulting polymer may be assigned a different CAS number; it would be considered a candidate for modular assessment as an analogue.

3.4 Criteria for determination of structural similarity

The following requirements are essential for a chemical to be considered *prima facie* to be structurally similar to another:

- contains some identical substructure that may play a critical functional role, such as defined in the USEPA TSCA New Chemicals Program Chemical Categories⁷;
- has similar molecular weight (carbon chain homology allows +/- 3x (-CH₂- radical) where carbon chain length exceeds 6)⁶;
- has similar molecular properties e.g. lipophilicity, electronic or steric parameters.

4. GUIDELINES AND EXAMPLES (OPPORTUNITIES FOR USE OF ANALOGUE ASSESSMENT)

The following case examples are types of structural analogues where modular assessment may allow for a reduced level of regulatory assessment input. The notified chemical will have both a similar structure and pattern of activity to an analogous chemical already assessed by NICNAS.

4.1 Salts

Salts often demonstrate a similar pattern of activity because the active chemical form is independent of the cation found in the preparation, and consequently identical *in vivo*. Salts formed when the hydrogen of an acid is replaced by an alkali metal or a cation of equivalent solubility (e.g. NH₄⁺) would be suitable for assessment under this category. Thus the Na⁺ salt is reasonably expected to be closely similar in activity to that of the K⁺ salt but quite different in activity to the Pb⁺ salt, the latter not being considered an analogue.

4.2 Homologues

A homologous series⁸ of chemicals may be structurally similar differing only in carbon chain length. Close chemical similarity will usually involve a degree of expert judgement, and analogue data should not be used for close homologues containing only a few carbons if the partition coefficient differs by more than a factor of two. Often, with the exception of methyl- and ethyl-, the chain length will have little effect on the pattern of activity and the assessment of homologues greater than C4 can be used for other chemicals in the series differing by less than 3 additional methylene radicals. Where there are more than ten carbons in a chain, homologues with addition or subtraction of 4 or more methylene radicals, which should not affect the activity pattern significantly, are regarded as acceptable analogues.

4.3 Structural and positional isomers⁹

Positional isomers have the same empirical formula, and acceptable analogues would include unchanged chemical functional groups and at least a single variation

(resulting in, or a change) to the branch point of a hydrocarbon chain, for example; normal-, iso- and anteiso- isomeric forms, or a change to the aromatic ring substitution position. However, in heterocyclic ring systems, both the ring size and the number and ring position of heteroatoms should not change.

4.4 Stereoisomers¹⁰

Optical¹¹ and geometric isomers¹² may be a group of chemicals suitable for analogue assessment if the biological function of the isomers is similar. While the pattern of activity of stereoisomers is often similar, numerous examples where stereoisomers behave very different metabolically require that the chosen animal toxicity endpoint of the proposed analogue be no less than half that for the previously assessed compound (i.e. that the new compound be at most twice as toxic as the previously assessed analogue). Thalidomide, for example, has teratogenic effects only demonstrated to be the responsibility of one of the two enantiomeric forms.

4.5 Bio-isosterism¹³

Chemicals related by a simple recognised change between two known bio-isosteric groups may be suitable analogues if both the K_{ow} and toxicity end-points are within the general limits prescribed in the criteria; 0.3 order of magnitude ($\pm 2x$).

4.6 Essential Oils

Often essential oils from plants of the same species may be regarded as different chemicals (with different CAS numbers) if geographical separation has resulted in slightly different chemical profiles. Often these differences may have little or no impact on the pattern of activity of the chemical.

4.7 Fatty Acid Resins

In many cases, chemicals that have a fatty acid chain such as alkyd resins, the fatty acid is not a determinant of chemical properties. Where the saturation profiles are similar (for example in the case of sunflower oil and soybean oil, or tung oil and linseed oil), one fatty acid may be substituted for another without significantly changing the properties of the chemical.

4.8 Animal/Plant Derived Fatty Acids

Fatty acid saturation profiles derived from animals and plants differ slightly; in cases where the saturation profile of the fatty acid has little impact on the pattern of activity (for example an organo-clay compound), either type may be considered a suitable analogue for the other.

4.9 Inseparable Mixtures

Where the chemical exists in an inseparable mixture of two or more structurally similar chemicals with different CAS numbers, the chemical of highest concentration is assessed as a standard notification with the others treated as analogues of the first assessment where the concentration exceeds 1%. The

toxicological assessment will be performed using information on the mixture rather than the notified chemical.

5. ASSESSMENT PROTOCOLS FOR ANALOGUES

It is proposed that, where a notifier believes that a close structural relationship exists between a notified chemical and one previously assessed by NICNAS (including assessed chemicals listed on AICS), a minimum data package would be required, which would include:

- Scientific justification for consideration of the chemical as an analogue;
- Details of proposed use, public and environmental exposure;
- Minimum physicochemical data on the notified chemical;
- Minimum toxicological data on the notified chemical; and for standard notifications; and
- Minimum environmental data on the notified chemical.

The notifier would still be obliged to provide all available data relevant to the normal scheduled data requirements for the notified chemical. The minimum data requirements for toxicological and environmental endpoints are suggested above under 'determination of analogy', noting a minimal requirement for animal studies. Minimum physicochemical data for chemicals and polymers respectively include:

- melting (or boiling) point, water solubility and partition coefficient; and
- density, particle size and water solubility.

5.1 Tier 1 Analogue Assessment (Minimum Testing Packages)

The most streamlined analogue assessment process would be available for chemicals where analogy has been demonstrated, and accepted by the regulator as meeting the requirements for the minimum data package. Furthermore, the mode of use of the chemical and expected public exposure is such that data beyond the minimum dataset is not considered necessary. It is envisaged that such an assessment strategy would allow for completion of the assessment within a similar time frame to that of Early Introduction Permits (28 days) when similar use patterns are proposed. A longer time period (but less than the current 90 days) will apply when different use patterns are proposed, reflecting the need for a separate risk assessment using the hazard data from the previously assessed chemical.

Close structural similarity together with closely similar physicochemical properties will provide an adequate basis on which to assess a chemical nominated for a limited notification where a full data set is available for its analogue. For standard notifications there is a greater need to consider the ecotoxicological implications, requiring assurance that the aquatic toxicity of the new chemical is not significantly greater (preferably less than double) than the analogue. In many cases, similar toxicity could be demonstrated by argument, with reference to the partition coefficient and mode of action of the new chemical.

For chemicals with a specific mode of action such as biologically active chemicals, aquatic toxicity data would be needed to demonstrate analogy when those chemicals are nominated as standard notifications. Argument based on a risk/hazard-based approach may be accepted *in lieu* of data. Thus if the analogue chemical has a low

PEC/PNEC ratio (say 0.001 or less; a wide margin of safety in the aquatic environment), then the need for additional data would be less than when the safety margin is smaller (say a PEC/PNEC of 0.1 or higher). The PEC/PNEC ratio would be determined for the most sensitive organism and where the ratio exceeds a critical threshold of 0.1 for the analogue, toxicity testing for the notified chemical in the same organism would be indicated.

It is intended that “umbrella-ing” of several chemicals will be possible. For example, a notifier submitting a sodium salt may nominate other salts such as the potassium and ammonium salt which may also be expected to be imported/manufactured in the future. A notifier may nominate chemicals which are analogous to a previously-assessed chemical to which they have access to the assessment report. In the case where a new chemical and several analogues are notified together, the notifier will be required to nominate the primary analogue which will be assessed as a new chemical for which a certificate will be issued. It is proposed at this stage that each additional analogue will be treated as an “extension” to the original assessment certificate.

It is proposed that where a manufactured chemical consists of two or more inseparable analogues, the chemical may be assessed in the following manner:

- (i) The chemical of the highest concentration is the ‘primary’ analogue, and is notified as a Standard or Limited Notification based on existing criteria. This chemical would appear on the assessment certificate, the notification and assessment of which proceeds with usual timeframes and fees.
- (ii) Each additional chemical becomes the subject of an extension to the assessment certificate for the ‘primary’ analogue with appropriately reduced timeframes and modular fees.

If the notified chemical is deemed to be unsuitable for assessment as an analogue (i.e. the scientific justification for analogy between two chemicals does not demonstrate beyond doubt that the chemicals would be expected to have similar physicochemical, toxicological and environmental properties), the notifier will be required to notify under one of the existing notification categories.

5.2 Tier 2 Analogue Assessment

In cases where the proposed uses and/or the exposure population are significantly greater for the notified chemical, NICNAS may determine at the initial screening stage that further data on the ecological or human health effects would be required in addition to the minimum data package.

References.

1. Analogue: etymology, early 19th century, from Greek *analogos* proportionate.
2. Oxford English Dictionary; Analogue: 3. *chem*. A chemical compound, especially a drug, which differs slightly in structure and properties from its parent compound.
3. Oxford English Dictionary; Equivalent: 3. *chem*. Having the same capacity to combine or react chemically.
4. US Patent Office Manual of Patent Examination Procedure; section 2100 Patentability. http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2144_09.htm
5. US Federal Code; Definition of “controlled substance analogue”, 21 USC 802 (32) (A) <http://www.deadiversion.usdoj.gov/21cfr/21usc/802.htm>
6. Chemical Assessment Section, Australian Government Department of Environment and Heritage
7. USEPA TSCA New Chemicals Program Chemical Categories. <http://www.epa.gov/opptintr/newchemicals/pubs/chemcat.htm>
8. Hawley, The Condensed Chemical Dictionary; Homologous series: a series of organic compounds in which each successive member has one more CH₂- group in its molecule than the next preceding member.
9. Hawley, The Condensed Chemical Dictionary; Isomer: One of two or more molecules having the same number and kind of atoms and hence the same molecular weight, but differing in respect to the arrangement or configuration of the atoms.
10. Hawley, The Condensed Chemical Dictionary; Stereoisomer: One of two or more molecules having identical chemical constitution, but differing in respect to the arrangement of the atoms or groups in space.
11. Hawley, The Condensed Chemical Dictionary; Optical isomer: Either of two kinds of optically-active three-dimensional isomers (stereoisomers).
12. Hawley, The Condensed Chemical Dictionary; Geometric isomer: A type of stereoisomer in which a chemical group or atom occupies different spatial positions in relation to the double bond.
13. Hawley, The Condensed Chemical Dictionary; Isosterism: Similarity in physical properties of elements, ions, or compounds, due to similar or identical outer shell electron arrangements.