Using Absolute and Relative Reasoning in the Prediction of the Potential Metabolism of Xenobiotics

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To be useful, a system which predicts the metabolic fate of a chemical should predict the more likely metabolites rather than every possibility. Reasoning can be used to prioritize biotransformations, but a real biochemical domain is complex and cannot be fully defined in terms of the likelihood of events. This paper describes the combined use of two models for reasoning under uncertainty in a working system, METEOR—one model deals with absolute reasoning and the second with relative reasoning.

INTRODUCTION

This paper discusses the distinction and interactions between absolute and relative reasoning under uncertainty and illustrates the use of both in a system for predicting potential metabolic pathways for xenobiotics, METEOR.[1] We term reasoning about the level of belief in an isolated event or conclusion with respect to an externally defined set of values, "*absolute* reasoning", and reasoning about comparative likelihoods in a set of competing events or conclusions, "*relative* reasoning". Two examples should make the distinction clear: the statement "A is probable" we classify as belonging to absolute reasoning, whereas the statement "A is more likely than B" belongs to relative reasoning.

Our previous work with regard to reasoning under uncertainty had been in the prediction of toxicity of chemicals, where it is necessary to answer questions of the kind, "How likely is it that this chemical will be toxic?" To make predictions about metabolism, METEOR needed to be able to answer questions of the kind, "Which of these reactions is more likely to predominate in this situation?" It has therefore been necessary to consider how relative reasoning should behave and how relative and absolute reasoning should interact.

For absolute reasoning, METEOR uses the model described in the preceding papers in this series.[2,3] This paper describes the reasoning system used in METEOR version 6.0 to deal with relative reasoning.

ABSOLUTE AND RELATIVE REASONING

Models based on absolute or relative reasoning, when they are both complete, should be wholly concordant. However, this can only be guaranteed when there are equal and equivalent data-points in both the absolute and relative hierarchies and the domain is fully defined. If the degree of graduation of the two hierarchies differs and/or the domain is not fully defined, then there is uncertainty and the two models may not describe each other—the greater the uncertainty, the less dependably they will do so.

For example, in METEOR the words 'probable' and 'plausible' are used to label two, adjacent levels of belief in the absolute reasoning model.[3] The word 'probable' is defined to mean that there is at least one strong argument that a proposition is true and there are no arguments against it, and the word 'plausible" is defined to mean that, even though there may be arguments for and against a proposition, on balance the weight of evidence supports it. Given these definitions, if we have a higher level of belief in Z than Y and Y is 'plausible', it does not follow that Z must be 'probable', only that our level of belief in Z is 'plausible' or greater; there may be more finely graded absolute levels of belief encompassed by the definition for 'plausible' which allow us to have a greater level of belief in Z over Y without obliging it to be 'probable'.

Conversely, suppose that A is 'probable' and B is 'plausible'. Setting aside potential uncertainty about the validity of this information, it is possible to state that our belief in A is greater than that in B but not how much greater.

RELATIVE REASONING

It is necessary to be clear about the intended implications of a statement like "Y is more likely than Z"—is it a statement only about the relative, independent, *potential* likelihoods of Y and Z, or should it imply that if Z occurs then Y must occur? If there is a causal link between Y and Z, Z is more likely than Y, and Y is a certainty, then Z must also be a certainty, but there are cases where this interpretation would be incorrect or inappropriate. Consider the statement, "There is more likely to be an earthquake in Tokyo today than in London". If an earthquake does occur in London today, this does not mean that one must occur, or is any more likely to occur in Tokyo today. In our model, relative statements do not imply interdependence—a statement such as "Y is more likely than Z" means that a priori Y is more likely than Z and not that the truth of Z has any implications for the truth of Y. The special case of causal dependency can be better expressed through statements in absolute reasoning ("If Z is true then Y is true").

Expressing the relative likelihoods of competing events is straightforward: when considering two events A and B

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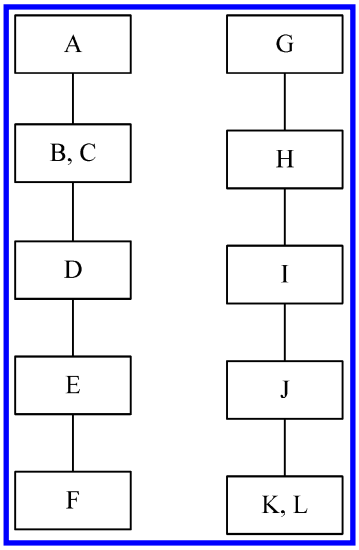


Figure 1. Two independent relative reasoning towers.

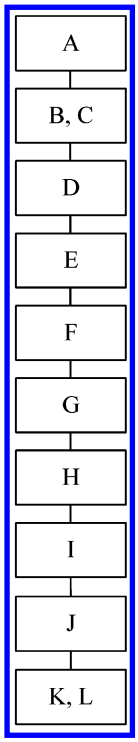


Figure 2. The result of stating that F is more likely than G.

we can state "A is more likely than B" (A > B) or "A and B are of equal likelihood" (A = B). Only two operators are needed as the relationship "A is less likely than B" can be expressed as "B is more likely than A" (B > A). A third situation—where there is no relationship between A and B—is implied by the absence of rules relating A and B. The relationships between events or conclusions can be expressed by placing them into one or more ordered lists, for which we use the term "tower". Items higher in a tower are more likely than those lower in the tower. In many domains of knowledge, such as knowledge about metabolic reactions, there will not be enough information for all items to be included in a single tower. More usually there will be several small towers. If, with the advent of new knowledge, an item occurs in more than one tower it may become possible to merge the towers.

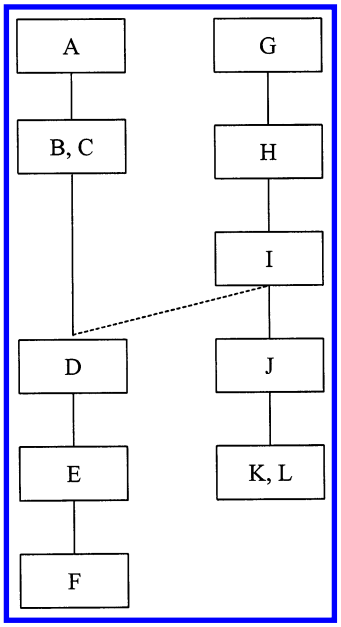


Figure 3. Linking I and D.

By way of illustration, suppose that we have information about twelve reactions, "A" to "L". Separate relationships, such as A > B, B = C, B > D, D > E, E > F, G > H, H > I, I > J, J > K and K = L, can be represented as shown in Figure 1.

The distances between floors in the towers are drawn as equal, but this is not to imply that the true differences in relative likelihoods are equal. Their magnitudes are not known. It might be, for example, that "A is slightly more likely than B" and "B is a lot more likely than D". Our current model does not incorporate the representation of, and reasoning about, degrees of difference in relative likelihood. Furthermore, the levels of the top floors or basements of the towers are not set in absolute terms, and either tower could be at any level relative to the other—the top floor of the first tower might be lower than the basement of the second tower, for example.

In the scheme in Figure 1 we have no knowledge about the comparison of likelihoods of any of the events in the first tower with any of the events in the second tower. If we learned that F was more likely than G, we would be able to merge the two towers by simply joining one on top of the other, as shown in Figure 2. This single tower would then describe the comparative likelihood of any pairing of the twelve reactions.

If on the other hand we learned of a new relationship, "I is more likely than D" (see Figure 3), there is now a connection between the two towers. By introducing this single new relationship (between I and D) we are also stating that I is more likely than E and F and that G and H are more likely than D, E, and F. There are however, no implied relationships between events (A, B, C) and (G, H, I), or (A, B, C) and (J, K, L), or (D, E, F) and (J, K, L).

These relationships make it impossible to merge the towers. Instead it is necessary to add a third tower. Figure 4a shows how this is represented in the program—the new relationship I > D is represented by a new tower [3]. There are often alternative ways in which the same information could be represented—for example, in this case, the one depicted in Figure 4b.

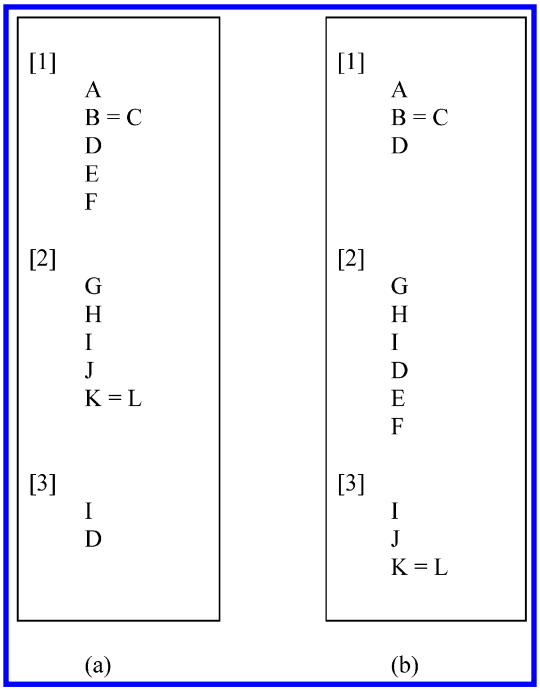


Figure 4. Two possible sets of towers representing the relationships shown in Figure 3.

LEVELS IN RELATIVE REASONING

Relative reasoning allows us to ask for the most likely events from a set of events, where "the most likely" means "those events for which there is no event more likely". In METEOR such events are said to be at Relative Reasoning level 1. Those events for which there is only one other more likely level would be at level 2 and so on. For example, in Figure 4a, A and G are at level 1, B, C, and H are at level 2. I is at level 3 because, although it is at the top of tower [3] it is below a level 2 event, H, in tower [2]. Similarly, D and J are at level 4 and so on. In METEOR the towers are built dynamically as each compound is considered with the result that, for example, if event A in tower [1] of Figure 4a is a biotransformation the defining biophore of which cannot be detected in the compound under consideration then B and C become level 1.

COMBINING ABSOLUTE AND RELATIVE REASONING IN METEOR

In the construction of the predicted metabolic profile (or reaction tree) in METEOR, first generation metabolites are created, and these child nodes of the query structure undergo reasoning assessment. Those that fall below the reasoning thresholds that have been selected by the user are removed from the tree. Each surviving child metabolite then undergoes a separate similar process of potential metabolite generation and refinement by reasoning until either no more metabolites can be produced or some other stopping condition is reached. Such stopping conditions include a maximum number of biotransformations in any one sequence or the production of metabolites from a phase II biotransformation.

The METEOR reasoning handles the absolute and relative models in independent stages. In version 6.0 of the program the option exists to use either one model or the other or both in combination (the default and recommended setting). If both models are enabled absolute reasoning is called before relative reasoning. This creates a bias toward the predictions of the absolute reasoning in that potential metabolites removed by absolute reasoning cannot be considered by relative reasoning. In a different application of the two models such a bias may not be appropriate.

In the first stage of the reasoning process, all biotransformations that have been applied and have generated a potential metabolite are fed into the absolute reasoning engine, which assigns a level of belief to each biotransformation. The user of the system can choose the lowest absolute level at which biotransformations should be retained. So, for example, if the user chooses a cutoff of 'probable', METEOR will retain only those biotransformations that the engine has ranked as (at least) probable, whereas if the user chooses 'equivocal' METEOR will retain those biotransformations that are ranked as at least equivocal (equivocal, plausible, and probable). In theory, in both cases biotransformations ranked as 'certain' would also be retained, but there are none so ranked in the current knowledge base for METEOR.

In the second stage of the reasoning process, all biotransformations that have survived from the first stage (those with an absolute level of belief equal to or above the chosen absolute cut off) are fed into the relative reasoning engine. The relative reasoning engine sorts them into their relative hierarchy with the most likely biotransformations at the top of the hierarchy. A relative reasoning cutoff is then applied reducing the number of remaining metabolites further.

MAKING RELATIVE REASONING CONDITIONAL

Relative relationships need not be fixed. Whether A is more likely than B or B is more likely than A may depend on circumstances. For example, in most mammals, the possibility of oxidation of a methyl group attached to an aromatic ring is high and would generally be favored over oxidation on the ring itself. This can be expressed in the rule, "benzylic oxidation is more likely than ring oxidation". However, in the dog benzylic oxidation is not so prevalent and the second reaction (if only comparing the two) would be more likely to predominate. The required relative reasoning rule would now be reversed—"ring oxidation is more likely than benzylic oxidation".

Linking absolute and relative reasoning would allow relative predictions to be made dependent on conclusions from absolute reasoning. The example of the previous paragraph might be expressed by rules such as, "if benzylic oxidation is probable then benzylic oxidation is more likely than ring oxidation" and "if benzylic oxidation is doubted then ring oxidation is more likely than benzylic oxidation". Statements of the form "If zzz is probable then it is plausible that xxx is more likely than yyy" would allow even greater flexibility. The current implementation of METEOR does not allow conditional rules of these kinds to be written or considered.

ABSOLUTE REASONING RULES IN METEOR

The absolute reasoning level for each biotransformation in METEOR expresses our level of belief that the biotransformation will occur in isolation, i.e., in the absence of competing reactions. Biotransformations which occur readily and are well documented in the literature are assigned higher levels of belief such as 'plausible' or 'probable', while those

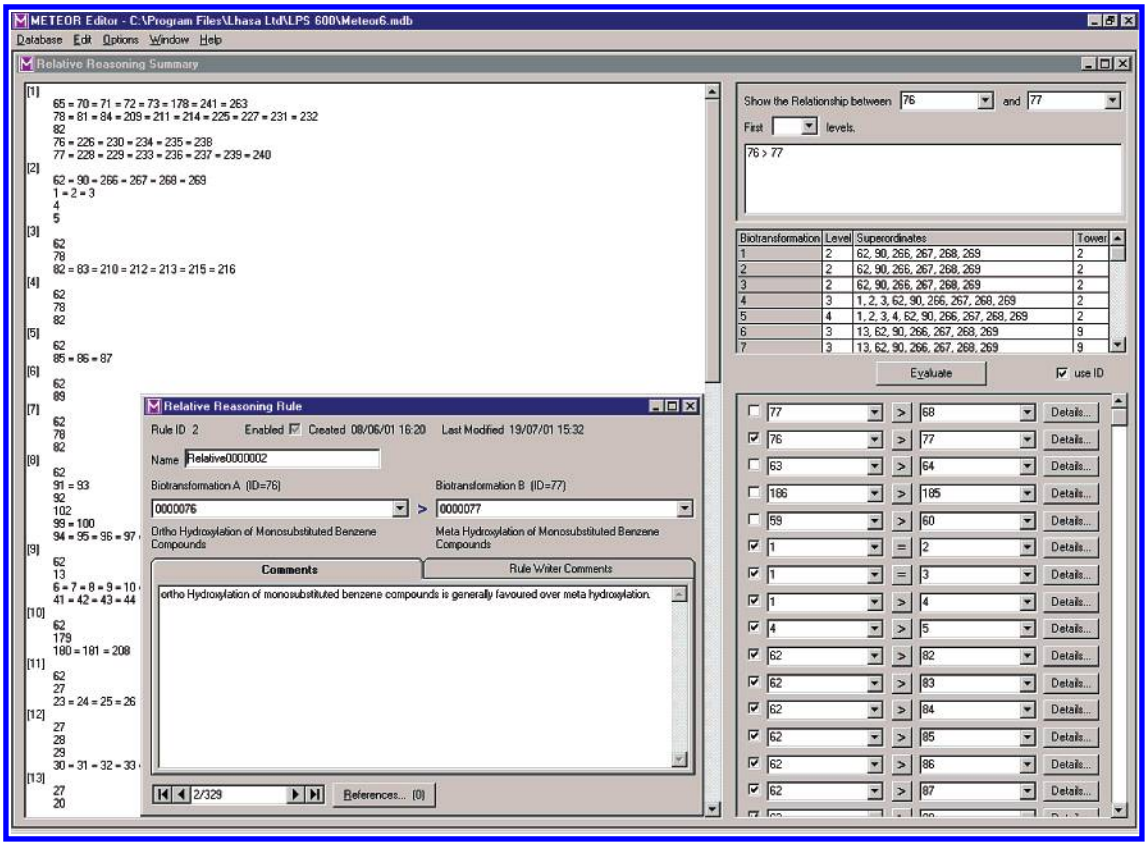


Figure 5. The editor for relative reasoning in METEOR.

which do not occur readily, and are perhaps speculative and poorly documented, are assigned lower levels such as 'doubted' or 'improbable'. Assessments are based, in part, on an understanding of the way xenobiotics are transported and bound in mammals.

The statements in the knowledge base which assign absolute levels of belief to biotransformations are conditional upon the lipophilicity of the substrate, as indicated by an estimated logP value. METEOR puts out a call automatically to a ClogP plug-in[4] for each substrate. For a substrate to undergo a biotransformation it must be able to present itself to an enzyme and become bound at the active site of that enzyme. This requires that the substrate should have intermediate lipophilicity so that it can both enter and leave lipid membranes easily.[5] Enzyme binding normally requires the substrate to have some hydrophobic regions, and substrates with these regions will have higher logP values than those without. So, having reached the enzyme, substrates with higher logP values are generally more likely to undergo biotransformation than those with lower logP values.[6] Rules in the knowledge base for METEOR assign an absolute level of belief to each biotransformation corresponding to high, medium, or low logP (default low/medium and medium/high cut off points are defined but can be changed by the rule writer or user). For example, a biotransformation may be probable at high logP, equivocal at medium logP, and doubted at low logP. These absolute levels of belief relate to the occurrence of biotransformations. Our belief that a particular metabolite will be formed is not necessarily the same as that in a biotransformation which generates it. Another biotransformation, or another sequence of biotransformations, may lead to the same metabolite. Neither do the absolute levels imply anything about the quantities of metabolites that biotransformations will produce.

RELATIVE REASONING RULES IN METEOR

The METEOR knowledge base contains generalizations about relationships between functional group types and regioselectivities within substrate types. Examples are "Primary alcohols are oxidized more readily than secondary alcohols" and "For monosubstituted benzenes, para-hydroxylation is favored over ortho-hydroxylation, and ortho-hydroxylation is favored over meta-hydroxylation".

The knowledge base editor for relative reasoning rules in METEOR is shown in Figure 5. The "Relative Reasoning Rule" window to the center of the figure is where a new relative rule is entered. Rules can be of two types: "A is more likely than B" (A > B) and "A is as likely as B" (A = B). The rule writer can add comments and reference data. To the right there is summary information for individual rules and their inter-relationships and to the left is a representation of the relative reasoning towers generated by the system.

The rulebase in METEOR was constructed using information about preferences within series of reaction types and the resulting relative reasoning skyline includes a tower dealing with carbon hydroxylation reactions, a second tower dealing with nitrogen oxidation reactions, another dealing with hydrolysis reactions, towers dealing with various phase II conjugation reactions, and so on. As our knowledge increases, and our biotransformation dictionary expands, we expect more crosscutting and integration of the relative reasoning towers to occur, improving the effectiveness of the approach.

A PRACTICAL EXAMPLE OF THE USE OF RELATIVE REASONING IN METEOR

N-Dealkylation reactions of amines and related functional groups are very common in the metabolism of drugs and other xenobiotic compounds. Because there is a rich literature documenting these reactions, and because we have a high level of belief that these biotransformations will normally occur for a given compound, these reactions are assigned confidence levels of 'probable'. The relative reasoning rulebase in METEOR is used to assess the most likely outcome of different biotransformations that may have the same confidence level. Thus, N-demethylation is considered more likely than loss of other, larger alkyl groups which in turn is considered more likely than oxidative scission of a nitrogen−carbon ring bond in cyclic amines and related compounds. Although there are exceptions to these general rules there is literature evidence to support this trend in reactivity. The conjoint use of two reasoning models in METEOR allows us to express the idea that although a series of reaction types may have a common associated level of belief or confidence, we can still prioritize among them when two or more of them can compete within the same query molecule, as the following examples illustrate.

RESULTS

Table 1 contains a summary of the comparison of the observed N-dealkylation products of four test compounds from the literature with predictions by METEOR for this reaction type at three different cutoff levels for relative reasoning. In three out of the four test conditions (compounds 1, 10, and 17) the level for absolute reasoning was set at 'probable', allowing generation of the metabolites of all biotransformations which were 'probable', or 'certain'.[3] In one out of the four test conditions (compound 21) the level for absolute reasoning was set at 'plausible'. No metabolites were found at the 'probable' level for this compound because of its lower calculated logP value. The reasoning engine ranked all N-dealkylation reactions as 'plausible' for this substrate. Only the first generation of metabolites was considered in each case. Where observed N-dealkylation products are discussed they were all quantitatively significant.

Example 1 − Sulforidazine (1). The antipsychotic drug sulforidazine (1) is an example of a xenobiotic compound containing all three of the structural motifs discussed above. Analysis of this compound limited to the top level of relative reasoning predicted formation of the *N*-desmethyl analogue (2) only. Relaxation of the relative reasoning constraint to the first two levels resulted in prediction of, in addition to (2), products associated with loss of the large alkyl group from the nitrogen atom of the phenothiazine ring (3), (4), and (5). Further relaxation to the first three levels led to prediction of products associated with oxidative disruption of the piperidine ring (6), (7), and (8) in addition to (2), (3), (4), and (5).

Loss of the *N*-methyl group was observed[7] in 24 h urine after oral administration of sulforidazine in rats (20 mg kg^{-1}). The *N*-desmethyl ring sulfoxide (9), formed either by S-oxidation of the desmethyl parent compound or by demethylation of the ring sulfoxide, was identified. Scission of the exocyclic bond connecting the alkyl chain to the phenothiazine ring or opening of the piperidine ring was not observed.

Example 2 − Venlafaxine (10). The antidepressant drug venlafaxine (10) is an example of a xenobiotic compound containing two of the structural motifs discussed above, namely the *N*-methyl group and the *N*-alkyl group. Analysis of this compound limited to the top level of relative reasoning predicted formation of the *N*-desmethyl analogue (11) only. Relaxation of the relative reasoning constraint to the first two levels resulted in the prediction, in addition, of products associated with loss of the larger alkyl group from the same nitrogen atom—the carboxylic acid (12), the alcohol (13), and dimethylamine (14). Further relaxation to the first three levels gave no further products.

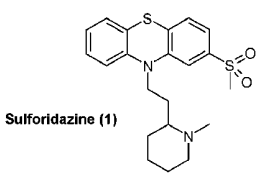
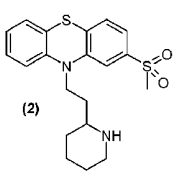
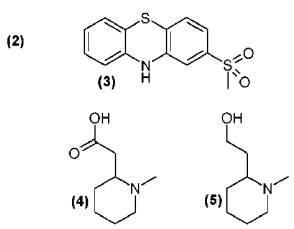
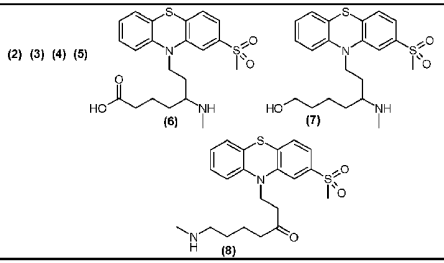
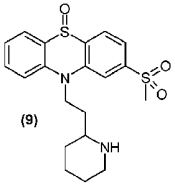
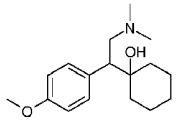
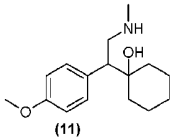
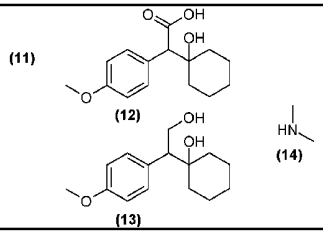
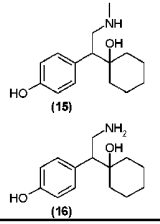
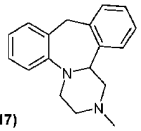
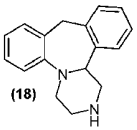
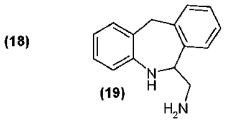
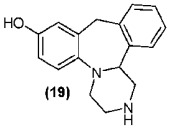
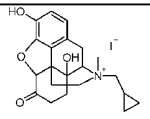
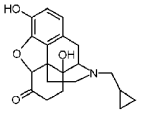
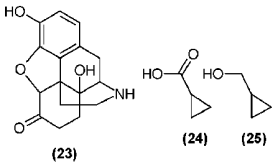
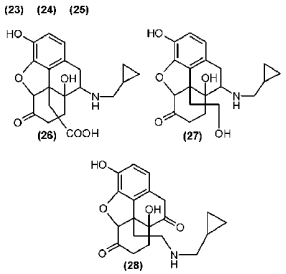
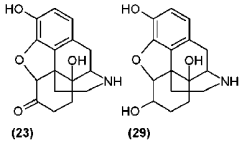
After oral doses of the drug to mouse/rat (22 mg kg^{-1}), dog (2 mg kg^{-1}), rhesus monkey (10 mg kg^{-1}), and human volunteers (50 mg kg^{-1}), between 85 and 97% of the administered dose was recovered in the urine, and most of this (>69%) was recovered in the first 24 h.[8] The major N-dealkylation metabolites identified were the glucuronides of the *N*,*O*-didesmethyl compound (15) in the mouse (15% dose) and the *N*,*N*,*O*-tridesmethyl compound (16) in the monkey. The alternative chain N-dealkylation leading to liberation of dimethylamine (14) or methylamine was not observed in any of the species studied.

Example 3 − Mianserin (17). The antidepressant drug mianserin (17) is another example of a xenobiotic compound containing two of the structural motifs discussed above, namely the *N*-methyl group and a cyclic amine. Analysis of this compound limited to the top level of relative reasoning predicted formation of the *N*-desmethyl analogue (18) only. Relaxation of the relative reasoning processing constraint to the first two levels resulted in the prediction, in addition, of the ring-opened diamine (19) via a biotransformation which expresses the sequential oxidative cleavage of both endocyclic nitrogen−carbon bonds between the two nitrogen atoms in the piperazine moiety in the parent compound. Further relaxation to the first three levels did not result in the generation of any further products.

After oral doses of the drug to rat (160 mg kg^{-1}), mouse (20 mg kg^{-1}), rabbit (80 mg kg^{-1}), guinea pig (25 mg kg^{-1}), and human volunteers (28 mg kg^{-1}), between 30 and >90% was recovered in the urine within 72 h.[9] The major N-dealkylation metabolites identified were the glucuronide of the *N*-desmethyl-8-hydroxy compound (20) in the rat (23% dose), mouse, guinea pig and rabbit (6−11% dose), and man (4% dose). Other *N*-desmethyl metabolites were found (conjugated and nonconjugated) in all species. Products associated with disruption of the piperazine ring were not observed in any of the species studied.

Example 4 − Naltrexonium Methiodide (21). The narcotic antagonist naltrexonium methiodide (21) contains two of the structural motifs discussed above, namely the *N*-alkyl group and a cyclic amine. Analysis of the neutral form of this agent, naltrexone (22) limited to the top level of relative reasoning predicted formation of products associated with the oxidative cleavage of the exocyclic nitrogen carbon bond, namely the *N*-desalkyl analogue (23) along with the carboxylic acid (24) and the alcohol (25). Relaxation of the relative reasoning constraint to the first two levels resulted in the prediction, in addition, of products associated with the oxidative disruption of the piperidine moiety (26), (27), and (28). Further relaxation to the first three levels did not result in the generation of any further products.

Table 1. Comparison of Observed N-Dealkylation Products for Four Test Compounds with METEOR Predictions for This Reaction Type at Variable Levels of Relative Reasoning

Test Compound	METEOR N-Dealkylation Predictions Relative Reasoning: "Grow from 1st Level"	METEOR N-Dealkylation Predictions Relative Reasoning: "Grow from 2nd Level"	METEOR N-Dealkylation Predictions Relative Reasoning "Grow from 3rd Level"	Observed N-Dealkylation Metabolites
 Sulforidazine (1)	 (2)	 (2) (3) (4) (5)	 (2) (3) (4) (5) (6) (7) (8)	 (9)
 Venlafaxine (10)	 (11)	 (11) (12) (13) (14)	No Further N-Dealkylation Metabolites Observed	 (15) (16)
 Mianserin (17)	 (18)	 (18) (19)	No Further N-Dealkylation Metabolites Observed	 (19) and other N-demethylated products
 Naltrexonium methiodode (21)  Naltrexone (22)	 (23) (24) (25)	 (23) (24) (25) (26) (27) (28)	No Further N-Dealkylation Metabolites Observed	 (23) (29)

The plasma of male rats administered with [15,16-^{3}H]-naltrexonium methiodide (21) by intravenous injection (4 mg kg^{-1}) was analyzed.[10] The major N-dealkylation metabolites identified were naltrexone (22), formed by N-dealkylation at the quaternary center, 7,8-dihydro-14-hydroxynormorphinone (23) and 7,8-dihydro-14-hydroxynormorphine (29), both formed via dealkylation, and loss of the cyclopropylmethyl fragment. These products were detected in a ratio of 32:5:68 but accounted for only 2% of the radioactivity in plasma, the rest being naltrexonium methiodide (21). Products associated with disruption of endocyclic bonds in the piperidine ring were not observed.

EXPERIMENTAL SECTION

Figure 5 and the results in Table 1 were taken from the program LPS version 6.0[1] running METEOR on a PC with a 731 MHz Intel Pentium processor and 256 Mb RAM running Windows NT version 4 with service pack 6. METEOR was activated with a license that gave access to the Relative Reasoning part of the knowledge base editor. LPS version 6.0 was written and compiled with Microsoft Visual Basic and Visual C++ version 6 with service pack 5. The values for logP were calculated using a ClogP plug-in.[4]

CONCLUSION

The combined use of absolute and relative reasoning in METEOR is at an early stage of development. Within the limitations of the current knowledge base, which we are currently extending, METEOR shows promise in directing the generation of potential metabolites toward those which might reasonably be expected.

ACKNOWLEDGMENT

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