UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
THE ADMINISTRATOR

EPA-EPEC-92-004

November 12, 1991
The Honorable William Reilly
Administrator
U.S.Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

SUBJECT: Science Advisory Board Evaluation of EPA's Research on Expert Systems to Predict the Fate and Effects of Chemicals

Dear Mr. Reilly:

The Fate and Effects Subcommittee of the Ecological Processes and Effects Committee of the Science Advisory Board has completed its review of research in progress on "expert systems for predicting the environmental fate and effects of chemicals". The Subcommittee reviewed three research programs on "expert systems" which are complementary and at different stages of development. Each of the systems relies on the physical and chemical properties of molecules to predict characteristics such as affinity for soil, water, or tissue and potential effects on biota, mode of toxic action, or metabolic products.

The Subcommittee met once on January 9-11, 1991 at the Athens Environmental Research Laboratory to review the research. The Subcommittee reviewed research on three expert systems: 1) SPARC (Sparc Performs Automated Reasoning in Chemistry) which estimates chemical and physical reactivity from molecular structure; 2) CRAMS (Correlations of Reactivity and Molecular Spectra) which predicts reactivity from spectroscopy analysis; and 3) QSAR (Quantitative Structure Activity Relationships) which will predict the mode of toxic action. As part of the review, the Subcommittee was asked to address the following charge:

1. Assuming that one can use chemical properties to predict chemical fate and environmental effects, does each system use chemical properties in a scientifically valid manner to make these predictions?

2. Is the documentation for using each system complete?

3. How well does each system "learn"?

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4. Are there other user needs that these systems could address?

The Subcommittee strongly endorses the present program of developing more potent structure activity relationships and methods to predict physical and chemical properties of compounds. However, the Agency should not rely solely on estimated values. The current approach of using fundamental molecular and atomic level information is an improvement over previous methods that used such information only for specific molecular properties. EPA has a continuing need for rapid estimation methods. This need is likely to increase rather than diminish in the near term as a result of two factors: i) a growing emphasis on review and regulation of existing chemicals by chemical class, rather than on a chemical-by-chemical basis as in the past; and ii) the establishment of a streamlined existing chemicals process capable of handling larger numbers of chemicals.

Documentation should be provided to assist the potential users of all three systems. Before such documentation is completed, each system should be subjected to rigorous testing, including representatives from EPA's toxics, pesticides, and hazardous waste programs as well as potential users from the academic and industrial research co as part of its development.

Two of the systems (SPARC and QSAR) can be "trained", however, due to the lack of documentation and testing, they must currently be considered as systems not capable of independent learning.

The overall approach seems to be state-of -the-art and should be useful not only for EPA efforts but will likely find use in other sectors of science, i.e., academic and industrial. The Subcommittee recommends that the SPARC, CRAMS, and QSAR expert system research programs be continued with an adequate level of funding for the initial development and testing.

The Subcommittee learned from the presentations by the Office of Pesticides and Toxic Substances that TSCA has no minimum data requirement for applicants in the Premanufacturing Notice program. It would be useful if the Agency were provided with basic data of known quality for all PMN chemicals. One way to achieve this would be for the Agency to issue guidelines relative to these data requirements.

The Subcommittee appreciates the opportunity to conduct this scientific review and looks forward to receiving your response to the scientific advice we have offered.

Sincerely,

Dr. Raymond Loehr, Chairman
Executive Committee
Science Advisory Board

Dr. Kenneth Dickson, Chairman
Ecological Processes and
Effects Committee

Dr. Robert Huggett, Chairman
Fate and Effects Committee

United States
Environmental
Protection Agency

Science Advisory
Board (A-101)

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EPA

AN SAB REPORT: EVALUATION OF EPA'S RESEARCH ON EXPERT SYSTEMS TO PREDICT THE FATE AND EFFECTS OF CHEMICALS

PREPARED BY THE FATE AND EFFECTS SUBCOMMITTEE OF THE ECOLOGICAL PROCESSES AND EFFECTS COMMITTEE

ABSTRACT

This report presents the conclusions and recommendations of the U.S. Environmental Protection Agency's Science Advisory Board following a review of research in progress on "Expert Systems for Predicting the Environmental Fate and Effects of Chemicals". Three research programs were reviewed. SPARC is an expert system for estimating chemical and physical reactivity. CRAMS predicts reactivity parameters of organic chemicals from spectroscopic data. The QSAR has several expert systems within it, but for this review, the Subcommittee concentrated on the "Single Integrated Language for Chemicals" and the plans for predicting mechanisms of toxic action from chemical structure. The Subcommittee supports the continued development and vigorous testing of each system. The SPARC and QSAR systems were considered state-of-the-art. CRAMS is more preliminary and shows promise particularly in the area of predicting metabolites. EPA was cautioned on the premature designation of these as "expert" systems. Other comments and suggestions are offered in the report.

Key Words: Expert Systems; Structure Activity Relationships; Predictive Toxicology; Fate and Effects.

U.S. ENVIRONMENTAL PROTECTION AGENCY
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Under existing laws (Toxic Substances Control Act, Federal Insecticide, Fungicide, and Rodenticide Act, and others), the EPA is responsible for predicting and evaluating the environmental fate and effects of chemicals. Multimedia assessments (air, water, soil) are needed to adequately evaluate the potential risks to human health and the environment from exposure to chemicals. Assessments must include the potential for effects due to specific properties of chemicals and to both short and long term exposures. Hence, detailed knowledge of chemical properties and reactivity is required to provide a rational scientific basis for the assessment process. Research being conducted at EPA's Environmental Research Laboratories at Athens and Duluth is designed to provide predictive capabilities for these chemical and biological fate and effect parameters. Three expert systems were presented for this review, SPARC, CRAMS, and QSAR. Expert systems, in this context are interactive PC-based programs that can be queried by professionals to examine the chemical characteristics of unknown compounds to make predictions about their fate in the environment. In practice, expert systems should be able to recognize patterns and "learn" from each problem that it analyzes. The following are some of the major points concluded by the Subcommittee in their review of this research:

1. The Subcommittee strongly endorses the present program of developing more potent Structure Activity Relationships (SAR) and methods to predict physical and chemical properties. However, the agency should not rely solely, at the present state-of-the-art, on estimated chemical, physical, and biological properties in its evaluation of toxic chemicals.

2. The over-all approach being used in developing SAR tools seems to be state-of-the-art and should be useful not only for EPA efforts but will most likely find wide use in other sectors of science, i.e. academic and industrial.

3. The Subcommittee recommends that EPA modify issue a Guideline to require the submission of basic physical and chemical data with statements of their quality during the PMN application process.

4. The Subcommittee recommends that the programs be continued with adequate funding.

5. The evaluation of CRAMS should focus on the development of model equations. The state-of-the-art is a long way from being able to incorporate all of the necessary state variables into models. Therefore, the model and its outputs should be subjected to vigorous field testing.

6. EPA should complete the documentation for the QSAR system. If not already available, EPA should develop information on the thermodynamics,

theory, etc. necessary to evaluate the underpinnings of the estimation method.

7. The models and their outputs should be subjected to vigorous field testing as soon as possible.

8. The concept of molecular properties prediction via structural correlation is an old idea which has been used in various branches of chemistry and chemical engineering. The current approach of using fundamental molecular and atomic level information in SPARC is an improvement over previous methods that used such information only for specific molecular properties.

9. The SPARC system has been labeled as an expert system but it is not with respect to teaching itself. The system has to be "trained" using hundreds of compounds. The so called "training" (which is equivalent to conducting a regression to obtain the various correlation parameters) requires precise empirical data and it has not been demonstrated that predictions can be accurately made for compounds that are outside the range of the chemicals used to "train" the system.

10. Care must be taken not to abuse the SPARC system by requiring it to perform functions for which it has not been "trained" or tested.

11. For biologically mediated reactions, state variables involving substrate concentrations, biological history of the population, impacts on biological rates and genetic shifts in the populations must all be considered.

12. User friendly expert systems for predicting chemical reactivity and environmental fate and effects of chemicals are needed now and they will play even more important roles in the future.

2. INTRODUCTION

The EPA administers several statutes (notably the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)) which require the Agency to estimate the fate and effects of chemicals. These assessments of fate and effects are often based on estimated values for specific properties of the chemicals. The Office of Research and Development (ORD) has been systematically working with the Office of Pesticides and Toxic Substances to assemble and integrate models that can predict specific chemical properties to estimate the environmental fate and effects of chemicals for inclusion in the Toxic Substances Inventory and for pesticide registration. This research has been an adjunct to other mainline programs and is centered in two laboratories: Athens, Georgia and Duluth, Minnesota.

2.1 Subcommittee Review Procedures

The Ecological Processes and Effects Committee (EPEC) of the Science Advisory Board received a request for this review from Dr. Michael Slimak, Deputy Director of the Office of Ecological Processes and Effects Research, ORD in June, 1990. After discussion by the committee, a proposal for a research in progress review of "Expert Systems for Predicting Fate and Effects of Chemicals" was submitted to the Executive Committee of the SAB. The Executive Committee assigned the review to EPEC. EPEC formed a Fate and Effects Subcommittee, which included a member of the Environmental Engineering Committee, and scheduled the review.

The Subcommittee received a research summary and scientific publications which described three "expert systems" (or systems intended to become experts systems): 1) SPARC (Sparc Performs Automated Reasoning in Chemistry), 2) CRAMS (Correlations of Reactivity and Molecular Spectra), and 3) QSAR (Quantitative Structure Activity Relationship). SPARC is an "expert" system for estimating chemical and physical reactivity. CRAMS predicts reactivity parameters of organic chemicals from spectroscopic data. The QSAR has several expert systems within it, but for this review, the Subcommittee concentrated on the "Single Integrated Language for Chemicals" and the plans for predicting mechanisms of toxic action from chemical structure.

The Subcommittee met January 9-11, 1991 at the EPA and USDA facilities in Athens, Georgia to receive briefings and a demonstration of the SPARC system. Following the meeting, the Subcommittee prepared a draft report. Unfortunately, none of these systems were available for testing by the Subcommittee members in their own laboratories.

2.2 Charge to the Subcommittee

Following the discussion of EPEC with Dr. Slimak, a formal charge for the review was developed and provided in December, 1990. The Subcommittee was asked to address the following questions:

1. Assuming that one can use chemical properties to predict chemical fate and environmental effects, does each system use chemical properties in a scientifically valid approach to make these predictions?

2. Is the documentation of the use and performance of each system complete? Is additional guidance needed to indicate under what circumstances the system may fail to accurately predict a value?

3. How well does each system "learn"? Are additional algorithms needed to back correct the estimates? Are additional approaches needed to identify outliers?

4. Are there other user needs that these systems could address?

3. THE SUBCOMMITTEE'S RESPONSE TO THE CHARGE

3.1 Scientific Basis for the Systems

The 1988 U.S. EPA document "FUTURE RISK: Research Strategies for the 1990's" (SAB-EC-88-040), contains a special section on sources, transport, and fate research of environmental contaminants. The document describes the importance of understanding fundamental environmental processes, improving the accuracy which with they can be modeled, and identifying emerging environmental problems. It further recognizes that one of the most effective approaches used in modeling environmental behavior of chemicals integrates data on physicochemical properties of the compound in question with hydrodynamic or aerodynamic transport models. This approach, which in large measure was formalized by the ERL-Athens, uses results from such laboratory measurements as aqueous solubilities, saturation vapor pressures, liquid and vapor molecular diffusivities, Henry's law constants, photolysis rates, UV absorption, octanol-water partition coefficients, etc. These data are then incorporated into various steady-state and time-dependent transport models. The fields of synthetic chemistry, chemical engineering, and pharmacology have, for quite sometime, successfully incorporated information on chemical properties in designing new chemicals, unit processes, and drugs. Additionally, studies aimed at understanding mechanisms of action at the molecular level of toxicity, carcinogenicity, mutagenicity, etc. clearly show that a knowledge of physical and chemical properties of both chemicals and targets is required. It is thus clear to the Subcommittee that the development of an ability to predict chemical properties for biological effects and environmental transport evaluations must be of high priority to EPA.

The Subcommittee thus strongly endorses the present program of developing more potent SARs and methods to predict physical and chemical properties. However, the agency should not rely solely, at the present state-of-the-art, on estimated chemical and physical properties in its evaluation of toxic chemicals. SARs and chemical property estimation methods should ideally be used to check experimental data for reasonableness, to pre-screen chemicals, to organize chemicals into different reaction or biological effects categories, and to generally improve the agency's capability of dealing with thousands of chemicals. A complete reliance on "desk exercises" is dangerous and will put EPA scientists in the position of making heroic estimations.

The chemical, engineering and pharmacological literature contains many techniques designed to estimate such properties as molar volume, boiling points, aqueous and multi-solvent solubilities, and vapor pressures. In addition, numerous investigations on chemical reaction rates and methods to predict these, especially in homogeneous gas and liquid phases, exist. These methods are often a blend of empirical, semi-empirical and thermodynamic approaches and each method may do particularly well (or poorly) for a selected subset of chemicals. It is probably fair to say that the above mentioned properties are very hard to predict a priori for chemicals that are very insoluble, have a low vapor pressure, exhibit moderate to

strong hydrogen bonding, and/or dissociate in liquids. Complicated molecular models, such as those that incorporate force field theory exist. However, a large dose of additional insight into fluid phase equilibria on a molecular level is needed.

Research developments at Athens and Duluth recognize all these past efforts and are designed to bring state-of-the-art insight into biological and environmental science applications. The Subcommittee agrees with the arguments presented on the need for these efforts and recommends that these be continued. Additionally, it appears that funding levels in the past have been rather uneven. The Subcommittee recommends that the programs be continued with adequate funding.

The effort for SPARC at Athens, although called an expert system, contains too many multivariate regression algorithms to be an expert system in the sense that it does not teach itself. The approach recognizes and uses formulations for basic intermolecular forces (electrostatic, induction, dispersion, and hydrogen bonding) to predict properties. However, although reduced in number over most present approaches, there still are several "adjustable" parameters which must be derived from learning sets. The functional group contribution approach combined with use of the reaction center concept is logical and is the only practical way to deal with thousands of chemicals. Thus the over-all approach seems to be state-of-the-art and should be useful not only for EPA efforts but will most likely find wide use in other sectors of science, i.e. academic and industrial. EPA should include members of this community in its beta testing of the SPARC system.

The biologically mediated reactions related to CRAMS involve a whole new set of model equations. State variables involving substrate concentrations, biological history of the population, impacts on biological rates and genetic shifts in the populations must all be considered. The state-of-the-art is a long way from being able to incorporate all of these state variables into models. Therefore, models generated in the near future will probably not be "smart" models that can mechanistically internalize error signals. The models and their outputs should be subjected to vigorous field testing as soon as possible. The individual modules could be placed on line as they are developed.

3.2 Adequacy of Documentation

The expert system for estimation of toxic effects reported on by ERL-Duluth is still under development. Therefore, this review must be seen as a review of research in progress. The documentation was complete in providing an overview of the knowledge-based system, especially in the form of output. However, the documentation available to the Subcommittee was incomplete for evaluating the performance of the expert system itself. For example, the SILC program and the SMILES program for establishing an appropriate computer code describing unique chemical strings addressable by other programs are very well described. But, the thermodynamics, theory, and other background information necessary to evaluate the underpinnings of the estimation method was not reviewed by the Subcommittee. However, it appears to the Subcommittee that the systems of

estimation are valid and represent the state-of-the-art.

The expert system (SPARC) for predicting chemical reactivity by computer is also still under development. The documentation for predicting UV-VIS absorption and ionization pKa is complete, rigorous and well done. The SPARC manual describes the steps and a minute part of the reasoning for the estimation of chemical and physical reactivity. SPARC is designed to estimate any reactivity parameter that depends on molecular structure. SPARC can estimate more than fifty different parameters but the theoretical and thermodynamic frameworks were only presented for UV-VIS absorption spectra. The ionization pKa's were not presented. We urge publication of these so that the approach can be subjected to additional peer review. There are still problems to be worked out. For example, better temperature functionalities and better ability to deal with nonideal systems (high ionic strength and multisolvent systems) are needed. The documentation offered does not permit an examination of the underpinning of the estimation procedures. However, the predictive capability of the software, as presented at the program review, is both state-of-the-art and comprehensive. For a program still in development, progress is excellent. Resources should be made available to complete the documentation and conduct extensive testing of the model.

3.3 System Performance

Subcommittee members were not provided with the opportunity to work with the software and individually evaluate the SPARC system. Therefore, some of the following comments are based only on the short demonstration that was presented.

The SMILES string code is well organized and the graphics software appears to be user-friendly and useful in viewing molecular structures. The molecular editor appears to be efficient and with sufficient flexibility to accommodate the experienced as well as the novice user. This system should prove itself useful in a variety of applications that make use of molecular structure information.

The concept of molecular properties prediction via structural correlation is an old idea which has been used in various branches of chemistry and chemical engineering. The current approach of using fundamental molecular and atomic level information is an improvement over previous methods that used such information only for specific molecular properties. The correlation of molecular reactivity parameters is a difficult task and the SPARC approach has thus far progressed to determining pKa values.

The SPARC system has been labeled as an expert system but this description is misleading in one sense, because SPARC does not learn without external stimulus. The system has to be "trained" using hundreds of compounds. The so called "training" (which is equivalent to conducting a regression to obtain the various correlation parameters) requires precise empirical data and it has not been demonstrated that predictions can be accurately made for compounds that are

outside the range of the chemicals used to "train" the system. The system is built with a reasonable user interface but it does not automatically learn as new runs are being conducted. The system appears to be one that, at present, requires handling by experts although running the system is not in itself a difficult task.

A robust system must be able to handle temperature dependence of various chemical properties. Thus, the robustness of the system should be tested by "training" the system using information from a few specific temperatures and subsequently attempting predictions at temperatures for which the system was not "trained". Similarly, predictions for compounds outside the range of those used to obtain the regression parameters should be used to test the performance of the system.

It appears that the system will execute on a standard desk top computer with a 386 or 486 processor (including a numeric co-processor). The regression (or system training) has not been ported to the desk top computer level and currently must be run on a mainframe. (This may have changed since our review). The Subcommittee cannot offer comments regarding the reliability, speed, or ease of use of the SPARC and CRAMS systems since it did not have the chance to test them. The EPA researchers hope that, in time, these estimation techniques will prove to be not only the nmost expedient, but also the most reliable means of chemical characterization.

As mentioned elsewhere, care must be taken not to abuse the system by requiring it to perform functions for which it has not been "trained" or tested. The main incentive for SPARC, at this time, should be to improve our understanding and check the reasonableness of reported values. To go any further would be a scientific mistake. The experience gained to date with the use of structure activity relations indicates that such correlations can often yield erroneous results if misused. Despite these concerns, the SPARC system as well as CRAMS could be potentially useful in determining trends and signalling problems when significant deviation is seen between the proposed prediction methods and other estimation methods and/or experimental data.

3.4 Agency's Need for Chemical Properties Data

Under existing laws (TSCA, FIFRA, and others), the EPA is responsible for predicting and evaluating the environmental fate and effects of chemicals. Multimedia assessments (air, water, soil) are needed to adequately evaluate the potential risks to human health and the environment from exposure to chemicals. Assessments must include the potential for effects due to specific properties of chemicals and to both short and long term exposures. Hence, detailed knowledge of chemical properties and reactivity is required to provide a rational scientific basis for the assessment process.

Approximately 70,000 industrial chemicals are listed by the EPA's Office of Toxic Substances (OTS). Parametric values for such properties as photolysis, hydrolysis, melting point and partitioning have actually been measured for only

about one percent of the chemicals in the OTS inventory. The cost of measurements required for the complete assessment of the probable behavior of a chemical in the environment has been estimated to range from $20,000 to $100,000. However, a basic physical/chemical data set would cost much less and most developed countries require manufacturers to measure and report elementary chemical properties such as solubility, K_{OW}, UV absorption, pKa, etc. The United States; however, does not require submission of the chemical characteristics data needed for initial risk screen.

The Toxic Substances Control Act (TSCA) clearly distinguishes between new and existing chemicals. Under TSCA, premanufacture notices (PMNs) must be submitted to (OTS) for review before new chemicals can be manufactured or imported in commercial quantities. TSCA requires the submission of all relevant data "known or to be reasonably ascertainable" by the submitter, but there is no statutory requirement for any kind of testing as a precondition for approval. As a result, PMNs seldom contain all the data necessary for a screening level assessment of environmental fate, and often contain little or no useful information beyond the name and structure of the chemical. The Subcommittee believes that these data (molecular formulation, melting point and boiling point, aqueous solubility, vapor pressure, and octanol/water partition coefficient) are "reasonably ascertainable" and should be a minimum requirement.

The basic steps in the PMN process include the Chemical Review and Search Strategy (CRSS) meeting where chemical nomenclature, structure, properties, reactions and use are reviewed. The CRSS review is followed by the Structure Activity Team (SAT) screening level assessment of environmental transport and transformation and then a review of human health and ecological hazards. Easily accessed databases such as the Environmental Fate Data Base are routinely searched prior to CRSS for data on analogs of the PMN chemical as well as the chemical itself, but data are seldom found. Moreover, even when data are submitted with the PMN or located in a pre-CRSS search, they are often of uncertain quality. Thus, early in the PMN process there is a need for reliable estimate of key physical/chemical properties and chemical reactivity, including biodegradability. In this regard, it would be useful if the Agency were provided with basic data of known quality for all PMN chemicals. One way to achieve this would be for the Agency to issue Guidelines relative to these data requirements.

From a technical standpoint, it would be favorable for the Agency to receive data during the PMN application and reivew process to allow better use of models.

EPA has a continuing need for rapid estimation methods. This need is likely to increase rather than diminish in the near term as a result of two factors: i) a growing emphasis on review and regulation of existing chemicals by chemical class, rather than on a chemical-by-chemical basis as in the past; and ii) the establishment of a streamlined existing chemicals process capable of handling larger numbers of chemicals.

Because of the inadequacy of existing physical/chemical properties databases and the lack of a requirement for industry submission of data required for initial risk screen of the potential adverse effects of new and existing chemicals, the Agency must develop and depend on methods for estimation of the parameters needed. At present, much of the chemical properties data used in chemical risk assessment is highly questionable and often obtained by "back-of-the-envelope" methods. Individual experience and scientific expertise, both of which are highly variable, play too large a role in the process. Hence, user friendly expert systems for predicting chemical reactivity and environmental fate and effects of chemicals are needed now and will play increasingly important roles in the future. Methods must be developed to scientifically determine whether compound A or B is a better analog of compound C. Otherwise, chemical risk assessment will never progress past chemical specific analysis, and the sheer numbers of chemicals will prevent the Agency from accomplishing its public mandate.

4.0 SUMMARY OF RECOMMENDATIONS

It is clear to the Subcommittee that the development of an ability to predict chemical properties for biological effects and environmental transport evaluations must be of high priority to EPA. The Subcommittee thus strongly endorses the present program of developing more potent SAR and methods to predict physical and chemical properties. The following list of recommendations should be pursued as part of the continuing development of these expert systems.

1. The Subcommittee recommends that the agency not rely solely, at the present state-of-the-art, on estimated chemical and physical properties for which the systems have not been trained, but rather to use the estimated values to improve understanding of the system capabilities and to check the reasonableness of reported values in their evaluation of toxic chemicals.

2. The Subcommittee recommends that EPA modify issue a Guideline to require the submission of basic physical and chemical data with statements of their quality during the PMN application process.

3. The Subcommittee recommends that the programs be continued with adequate funding.

4. EPA should involve other sectors of science, i.e. academic and industrial, in a broad review and testing of these systems.

5. The evaluation of CRAMS should focus on the development of model equations. The state-of-the-art is a long way from being able to incorporate all of the necessary state variables into models. Therefore, the model and its outputs should be subjected to vigorous field testing.

6. EPA should complete the documentation for the QSAR system. If not already available, EPA should develop information on the thermodynamics, theory, etc. necessary to evaluate the underpinnings of the estimation method.

7. The Subcommittee urges the EPA to complete its testing of the SPARC system and develop full documentation on the mechanistic underpinnings for each of the systems.

8. EPA should develop user friendly expert systems for predicting chemical reactivity and environmental fate and effects of chemicals that include methods to scientifically determine whether a known compound A or B is a better analog of the fate and effects of an unknown compound C.