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INVITED REVIEW

Advancing Computational Toxicology in a Regulatory Setting: A Selected Review of the Accomplishments of Gilman D. Veith (1944–2013)

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Abstract

With the passing of Dr. Gilman D. Veith on August 18, 2013, the research community lost one of its true visionaries in the development and implementation of alternative in silico and *in vitro* toxicology models in human health and ecological risk assessment. His career spanned more than four decades, during which he repeatedly demonstrated vision and leadership to advance alternative testing and assessment research and to guide the adoption of research accomplishments into U.S. and international chemical regulatory programs. His ability to advance toxicological and environmental exposure research, and associated quantitative structure–activity relationships (QSARs), for application in environmental regulatory decision making was achieved by a focus on establishing a transparent, mechanistic understanding of the chemistry and biology underlying alternative experimental and mathematical models. Dr. Veith was a pioneer of the application of alternative methods, especially QSAR to industrial chemicals, which traditionally lacked the experimental data already available for pesticides and pharmaceuticals. His lifelong vision and leadership were recognized by a number of awards, including the Henry J. Heimlich, M.D., Award for Innovative Medicine in 2010. Through Dr. Veith's accomplishments, the use of alternative approaches in toxicity testing and risk assessment was implemented in the 20th century. His leadership also provided the scientific and regulatory framework for developing and applying *in vitro* and in silico techniques in what is now coined as 21st-century toxicology.

Key words: chemical risk assessment and risk management, *in vitro* testing, predictive toxicology, quantitative structure–activity relationships.

Introduction

Born and raised in Minnesota, Dr. Gilman D. Veith received his undergraduate education at Augustana College in South Dakota and was later awarded a PhD in water chemistry by the University of Wisconsin–Madison in 1970, where he became a member of the faculty. In 1972 he joined the Office of Research and Development's laboratory, U.S. Environmental Protection Agency (EPA), in Duluth, Minnesota. Spanning 30 years of public service with EPA through 2003, his accomplishments in leading multidisciplinary research teams to successfully address a broad spectrum of environmental protection challenges facing the United States and global partners are almost

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impossible to summarize. In this article, we attempt to highlight Dr. Veith's vision, leadership, and focus to advance the development and implementation of alternative methods in the mission of environmental protection during his career at EPA, the Organisation for Economic Cooperation and Development (OECD), and the International QSAR Foundation (IQF) (www.qsari.org).

EPA Years

Dr. Veith joined EPA's Environmental Research Laboratory–Duluth (now known as the Mid-Continent Ecology Division) in 1972, undertaking research on the bioaccumulation and effects of polychlorinated biphenyls and other persistent, hydrophobic chemicals in aquatic ecosystems. His early research in this area[1–4] and continued interest and scientific insights throughout his EPA service provided opportunities for numerous scientists to advance a nationally and internationally recognized research program in the Duluth laboratory that continues to this day.[5] His contributions and the follow-on bioaccumulation research program that he began provided the foundation with advancing regulatory approaches to protect human health and the environment from bioaccumulative chemicals.[6,7]

In 1975, Dr. Veith began the quantitative structure–activity relationships (QSAR) research program for EPA in anticipation of the passage of the Toxic Substances Control Act (TSCA; P.L. 94-469) in the United States. With the enactment of TSCA, agency risk assessors needed ready access to information and new innovative methods to determine or estimate the fate and toxicity of new industrial organic chemicals submitted under the premanufacture notification program, as well as existing chemicals on the TSCA inventory. Under TSCA, companies were not required to test new chemicals before notifying EPA, an approach that challenged EPA to assess the potential risks in the absence of test data. The U.S. scheme differed from that in Europe, where new chemical notices included a required ''minimum premarket dataset'' of health and environmental testing. The common wisdom at the time was that this part of TSCA could not possibly work given the uncertainties and unknowns. Establishing a scientific means for EPA to bridge this new chemicals ''data gap'' was the heart of the challenge he faced. Through collaboration with colleagues in the EPA's Office of Toxic Substances (now known as the Office of Pollution Prevention and Toxics), he developed and implemented a research program that established the means to evaluate the potential fate and effects of tens of thousands of industrial chemicals for which little or no empirical data existed.

The foundation of the research program that Dr. Veith led was his recognition that the research needed to define and meet the scientific uncertainties and gaps within the applied context of EPA's legislative and regulatory framework—this was essential to ensure that resultant research products could be practically implemented in a way to meet the regulatory needs under TSCA. His focus on science for a purpose and the public good was combined with his scientific vision, intellect, and leadership that brought together scientists in EPA and other federal and international governmental agencies as well as researchers in academia from around the world. By leading and empowering highly diverse groups of researchers in fields ranging from computational sciences to multiple fields and areas of specialization in chemistry, biology, and toxicology, he created the environment to establish truly collaborative, multidisciplinary teams that created and implemented research programs and achieved prodigious results of practical utility. This resulted in accomplishments that could never have been imagined, much less realized, if the research had been undertaken by isolated teams or without a clear roadmap that brought all the components together in a way designed to meet both scientific and regulatory needs—from the computational and laboratory research to the delivery of databases, predictive models, and decision-support systems at the desk of the agency's risk evaluators and regulators. Tangible evidence of the applied success of his efforts and those by other QSAR experts in EPA can be seen in the widespread recognition that TSCA's new chemicals program, far from failing, is seen as the act's most effective and significant achievement over the past almost four decades.

Dr. Veith advanced the QSAR research program with a long-term view, but realized that clear, practical, and incremental steps were needed to be accomplished to establish and maintain an orderly and efficient delivery of information and tools for the agency's risk assessors to implement TSCA. This strategy also established an effective means to advance the research program, and integrate and optimize the diverse talents and skills of the research teams that were addressing different dimensions of increasingly complex problems. No matter what the chemical fate, exposure, or effect issue being addressed by the QSAR research program, four aspects were always brought into focus and integrated to address the specific challenge at hand. In a true concert of nonlinear research planning and execution, there was the need to (1) create and advance the means of communicating chemical structure, be it in two or three dimensions, to human beings and computers; (2) define the nature of the empirical fate, exposure, or toxic effect endpoints of regulatory interest in clear and unambiguous terms; (3) develop, typically in an iterative fashion, databases for the well-defined endpoints of interest for the chemical structure space of regulatory application; and (4) use the empirically derived data to establish the predictive (Q)SAR models that related the values of an endpoint of interest to appropriate features of chemical structure or physicochemical properties estimated from chemical structure. An overarching philosophy that helped integrate the research approach and establish credibility in the application of the resultant data and/or (Q)SARs in the regulatory setting was to establish a mechanistic understanding of the model development and interpretation of its outputs. The goal was to create understanding of the key chemical, biological, and toxicological properties and relationships, and then to create knowledge bases and QSARs that synthesized and relayed information and predictions that were clear and transparent. Through this approach, the research and the ultimate product, be it a knowledge base or a QSAR, can be described in a manner that enables the scientific or regulatory user the means to evaluate the mechanistic uncertainties, as well as statistical attributes, of empirical and predicted data in the context of the specific regulatory application. This philosophical approach to the research that began in the 1970s was the precursor to today's recognition and acceptance of QSAR tools and approaches by governments around the world and to the development of the OECD's principles

for the validation, for regulatory purposes, of QSARs (Schultz and Diderich, personal communication).[8,9]

We provide here highlights of key accomplishments that resulted from his leadership of the EPA QSAR research program.

Defining chemical structure and structure space

The development of the Simplified Molecular Input Line Entry System (SMILES) convention[10,11] revolutionized the world of computational chemistry by providing an easy-to-learn and convenient means of communicating chemical structure information to a computer. The QSAR program also developed a means of depicting each SMILES string in a unique format, allowing users to enter the chemical structure in any sequence. The unique SMILES string could then be used to link the chemical structure to database information (e.g., toxicity or fate data). The use of SMILES notation has been adopted by the drug and chemical industries as well as other federal and international agencies and is a common feature in both public and private chemical databases and computational tools. SMILES eventually led to the development of the Simplified Input Language for Chemists compiler,[12] a powerful tool that links substructure information to chemical or biological information such as biological degradation rates, mode of action (MOA) classifications, and/or estimates of toxicity. The ability to identify subgraph information allowed for the eventual development of expert systems to predict the effects a chemical may have on a biological system.[13–19]

Under the QSAR program, algorithms were developed to calculate molecular connectivity indices for any chemical structure and with any size subgraph. Before this, it was not possible to calculate these indices for multicyclic systems because the software did not exist. Since these indices can be computed for any chemical structure, the use of QSARs developed with molecular connectivity indices eliminates the need for extensive measured physical property data.[20–26] A major application of the molecular connectivity research was to develop a means to visualize the discrete industrial chemicals in the TSCA inventory, which was essential for establishing a rational means of identifying training set chemicals for QSAR development. Using this approach, over 19,000 substances were plotted in a multidimensional hyperspace, based on their molecular topology and graph theoretical indices; training set chemicals for developing QSARs to predict acute toxicity to fish were subsequently selected from a diversity of chemical ''neighborhoods.''[26] This approach ensured that the database covered a wide range of structure space, and thereby a wide range of possible MOAs[27,28] relevant for the chemical universe of regulatory interest, and laid the foundation that others continue to follow.[19,29,30]

In addition to advancing methods for defining chemical structures, and chemical structure space, based on two dimensions, he realized that the ability to predict many chemical and toxicological properties would require the means of depicting chemical structure in three dimensions. In the mid-1980s, the QSAR program began the development of CONCORD,[31] which was a precursor to subsequent efforts to define and quantify steric and electronic characteristics of chemical structure for use in a variety of QSAR applications.[32–34]

Knowledge bases and QSARs: physicochemical and environmental fate properties

Under Dr. Veith's direction, various knowledge bases and computational methods for accessing or estimating physicochemical properties were refined, or new methods were designed. These properties, such as boiling point, vapor pressure, heat of vaporization, pKa, water solubility, molecular surface area, molar volume, and octanol-water partition coefficient were identified as critical properties needed to help predict environmental fate and/or toxicological properties. These knowledge bases were first made available publicly in the 1980s and more recently have been merged into other publicly available systems such as EPISuite[35] and the OECD's QSAR Toolbox.[36] Just a few notable examples of widely used knowledge bases and predictive models that were derived under his leadership and partnerships include the ClogP model (Biobyte, Claremont, CA) to predict the octanol-water partition coefficient, a bioconcentration model that predicts a chemical's bioconcentration potential in fish from the octanol-water partition coefficient,[2] and an expert system that estimates the biodegradation rate of chemicals.[13,14,37]

Knowledge bases and QSARs: toxicological properties

A hallmark of Dr. Veith's leadership was that the development of QSARs necessitates the availability of reliable toxicity data sets based on well-documented, uniform testing protocols, and well-defined and unambiguously quantified endpoints. Dr. Veith's initial strategy was the development of a database summarizing aquatic toxicity information published in the open literature, which eventually became the EPA's ECOTOX database.[38,39] Although this database met some of the requirements for QSAR development, he realized the need for a new data set, developed under very controlled test protocols, specifically designed for use in building robust QSAR models. To this end, high-quality toxicity data (i.e., fathead minnow 96 h LC50 values) were systematically developed for 617 industrial chemicals, and QSARs were subsequently established based on known or hypothesized MOAs.[27] Through this research approach, the teams and programs led by him moved beyond QSARs based on common structural features, used in typical chemical classification schemes, to MOA-based QSARs that provide more reliable and toxicologically interpretable model predictions. Dr. Veith's philosophy was that QSAR models needed to be developed based on chemicals that shared a common MOA. This fundamental perspective, which is now considered ''best practice'' in QSAR development,[36,40] was met with some degree of skepticism in the 1980s and 1990s. As summarized by Russom et al.,[28] as his seminal article on a QSAR for industrial chemicals based on a narcosis MOA was being published,[41] the QSAR program had already embarked on a multipronged approach to build a systematic acute toxicity and MOA knowledge base to develop mechanistically based QSARs reflective of the industrial chemical structure space (see the Defining Chemical Structure and Structure Space section). The fathead minnow database of 96 h LC50 values has been a major component of the training sets behind many QSAR modeling and structure fragment tools in use today (e.g., EPA's ECOSAR[35] and the OECD QSAR Toolbox[36]). This is due in part to its

transparency and public availability,[28] but its usefulness in QSAR modeling can mainly be credited to the strategic approach taken in the development of the database. The express purpose of the fathead minnow database was to build relevant and reliable QSAR models based on data that covered a wide range of structure space and thereby a wide range of possible modes of toxicity. All toxicity tests were conducted in the same laboratory following standard test methods. Both the dilution water and fish used were from a single source. Chemicals used were of the highest purity, with all treatment concentrations measured under stringent data quality objectives. By controlling for these factors, variability in the test results was minimized and thereby increased confidence that variation in toxicity was related to variation in chemical structure and associated toxicological properties.

The fathead minnow database is not the only collection of high-quality study results available for use in the development of reliable QSAR models (see Bradbury et al.[42] and www.epa.gov/ncct/dsstox/ for other model data sets). What makes the fathead minnow database unique is that, along with mortality data, the database includes results from behavioral toxicity assessments,[43] studies on physiological responses in rainbow trout,[44,45] and joint toxicity of chemical mixture tests.[46] Using a weight-of-evidence (WOE) approach, the multiple data types were then used to assign an MOA to each chemical.[47] The MOA assignments benefited from the results of a 1988 EPA-sponsored workshop that brought together experts in the field of toxicology. The workshop yielded a series of articles that document the structural and physical/chemical attributes for MOAs associated with acute exposure (e.g., narcosis, uncoupling of oxidative phosphorylation, electrophilic reactivity, acetylcholinesterase inhibition, and voltage-gated sodium channel modulators).[48] The development and release of QSARs based on these MOA classifications is summarized in Russom et al.[27] and available online.[40] Subsequent and ongoing research using the same MOA approach, increasingly based on *in vitro* models to generate the well-defined toxicological endpoints, is being employed to derive QSARs or expert systems to predict toxic effects associated with electrophilicity,[32,49] oxidative stress,[50] and hormone receptor binding affinity.[16–19,51]

Dr. Veith's contributions to understanding and modeling chemical metabolism were set in motion before he left the agency. Consistent with his constant focus on designing research to address regulatory needs, he laid the groundwork for approaching what continues to be the ongoing need to predict xenobiotic metabolism. The problem is an especially challenging one, given that often analytical difficulties are encountered in measuring small but toxicologically significant chemical metabolites.[52,53] Early efforts inspired by Dr. Veith in the 1980s to establish databases of metabolites and transformation rates[54,55] were later followed by the building of a software tool with the computational capabilities needed to both systematically capture metabolism pathway data and provide data analysis tools to aid risk assessors.[56] The further development of the metabolism pathway (MetaPath) tool is now an internationally supported project of the MetaPath Users Group under the OECD Working Group on Pesticides. The development of metabolism simulators continues today both inside EPA and internationally.

OECD Years

In 2004, Dr. Veith accepted an appointment as science advisor with the OECD. As early as 1991, OECD had an ongoing activity in the area of QSARs for regulatory purposes. However, for a variety of reasons, including skepticism, progress in QSARs at OECD was slow before his involvement. He brought to OECD his understanding that for SAR and QSAR to succeed in a regulatory context, databases with experimental data were needed to be collected, tools to identify similar chemicals were needed to be developed, and a variety of QSARs were needed to be established.

OECD principles for the validation of QSARs

Dr. Veith contributed in many ways to move the QSAR program at OECD forward. One of his first missions as a member of the OECD Secretariat was to gain member country agreement on the best principles of QSAR validation.[8] He did this by building on the recommendations and conclusions of the international workshop held in Setúbal, Portugal, in 2002.[57,58] This workshop proposed the ''Setúbal Principles,'' which he, in collaboration with the workshop's organizers, further refined and which ultimately culminated in the adoption of the OECD principles for the validation, for regulatory purposes, of (Q)SAR models in November 2004.[8]

These latter principles state that to facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

1. A defined endpoint
2. An unambiguous algorithm
3. A defined domain of applicability
4. An appropriate measurement of goodness-of-fit, robustness, and predictivity
5. Mechanistic interpretation, if possible

These principles have since been recognized of having broad applicability and form the basis of developing and evaluating *in vitro* and *in vivo* bioassays and in silico models for regulatory application.[17,18,59–61]

Principle 1. Dr. Veith observed that most human health adverse effects measured in experimental studies do not lend themselves to QSAR because the *in vivo* endpoint measurements in the variation of biological activity are not directly related to variation in chemical structure. Therefore, while one could find associations between ''structural alerts'' and discrete toxicological phenomena (e.g., mutagen vs. nonmutagen, carcinogen vs. noncarcinogen, or skin sensitizer vs. skin nonsensitizer), results from *in vivo* mammalian toxicity tests are typically integrating numerous toxicokinetic and toxicodynamic processes, which makes it very difficult to develop QSARs that relate the potency of a group of chemicals' particular effect to attributes of their structures.

As he noted,[62] the challenge with most mammalian toxicity tests is that they are not designed to measure intrinsic variation with structure. While, with most fish toxicity assays the chemical's blood concentration is in equilibrium with exposure water concentration, oral exposure assays in mammalian studies, such as the mammalian oral 28-day repeat dose test, are conducted under non-steady-state conditions. Consequently, the observed toxicity could be a function of the

area under the curve or the maximum dose—this uncertainty in dosimetry in turn creates uncertainty in any QSAR model development (i.e., any QSAR model would incorporate the uncertainty in both the dosimetry expression and estimated potency inherent in the underlying toxicity data). In addition, mammalian *in vivo* assays typically report numerous phenotypic responses. These responses need to be carefully considered and specific endpoints defined before attempting QSAR development. A well-defined endpoint for QSAR development should also include an understanding of the underlying relationship between the endpoint of interest and the known or hypothesized MOA. For example, in mammalian oral repeat dose assays, ''liver toxicity'' lowest observable adverse effect concentrations (LOAECs) based on blood concentrations are sometimes reported; however, chemicals that cause liver fibrosis are probably acting through different toxicodynamic process than chemicals that cause liver steatosis. In the context of principle 1, compounds that cause liver fibrosis and those that cause liver steatosis should not be combined in the same QSAR.

The challenge to establishing a well-defined endpoint for QSAR development holds when developing and using *in vitro* bioassay models as well. However, well-designed and well-executed *in vitro* studies, based on mammalian or nonmammalian species, provide the means to measure well-defined endpoints associated with a molecular initiating event within an adverse outcome pathway (AOP) (see OECD[59] for a discussion of toxicity pathway and AOP terminology) that can provide the means of reliably relating variation in biological response with variation in chemical structure. As discussed in the AOP for protein binding leading to skin sensitization,[63,64] one key event that can be assessed *in vitro* and modeled in silico is dendritic cell activation.

Principle 2. The availability of inexpensive, high-powered computers in the 21st century allows what in the 1980s could only be done in minutes on a mainframe to be done in milliseconds on a personal computer, thus permitting the development of complex QSARs. Examples of such QSARs include multiple regression models where large numbers of chemical descriptors were screened, selected, and then used to develop QSAR models. Realizing that increased computer power allowed for a myriad of models, many of which were not ''transparent'' and lead to little more than ''black box'' predictions, he recognized the importance to have an unambiguous algorithm and strongly supported applying the principle of parsimony—use the simplest model possible.

Principle 3. Dr. Veith foresaw that for QSARs to be accepted in a regulatory setting, it is necessary to define the models' applicability domains. To assure the appropriate use of a QSAR model, and its predictions, it is important that the model's applicability domain be defined because predictions outside of this domain may lead to errors. To paraphrase him, a QSAR should only be used within the chemical structural space where the model makes predictions with high reliability. This principle is equally applicable to the development and direct use of *in vitro*[16–19] (as well as *in vivo*) assay data in a risk assessment and reflected in OECD test guidelines currently undergoing development.

Principle 4. Statistical evaluations of appropriate measurements of goodness-of-fit, robustness, and predictivity of models are certainly an important aspect of model development and implementation in a regulatory setting. He, however, cautioned against an overconcern with statistical parameters. He sensed that an emphasis on statistical parameters such as fit and internal predictivity measured, for example, by r^2 and q^2, respectively, could make QSAR development a curve-fitting exercise. The same concern applies to models using single-endpoint *in vitro* data to predict *in vivo* responses, where the more robust assessments employ external evaluation data sets or at minimum ''leave-N-out'' cross-validation algorithms.

Principle 5. The need to establish a mechanistic interpretation of the toxicological process and relationship to chemical structure was one of the hallmarks of his efforts at OECD. As he noted, much of the skepticism over QSAR comes from their inappropriate use for chemicals that elicit different MOAs. He strongly believed that models need to be grounded in a toxicology-based mechanistic interpretation. For example, chemicals with the potential to covalently bond with proteins have been shown empirically to be causally related to skin sensitization. Since organic chemicals react covalently with skin proteins in order to behave as a skin sensitizer, a model that uses a protein-binding descriptor is toxicologically relevant to skin sensitization.[65] Again, the same principle holds for understanding and relating endpoints and responses from *in vitro* assays to potential responses at higher levels of biological organization.[51,66]

OECD QSAR toolbox

Dr. Veith was a big proponent of the chemical category approach.[67] He envisioned how mechanistic information in the form of in silico, in chemico, and *in vitro* data could inform the formation of a chemical category. Once defined, *in vivo* data for category members could then be read-across to nontested member of the same category.

In 2006, the OECD QSAR program initiated the QSAR Application Toolbox project (later simply called the OECD QSAR Toolbox). Perhaps his greatest contribution while at OECD was his leadership in developing the OECD QSAR Toolbox.[36] The toolbox is a highly sophisticated knowledge base that functions as a rule-based expert system. As such, it is designed to solve toxicological problems with approximately the same rate of accuracy as do toxicologists themselves, retain and distribute information, enhance and clarify vague expertise, and save both time and resources. The toolbox, like other expert systems, includes a knowledge base of rules and parameters, and an inference engine. The inference engine is the software that processes the rules and informs judgments to arrive at a specific conclusion or prediction.

Dr. Veith envisioned the toolbox as software aimed at making practical QSAR applications readily available and accessible. The philosophy of the toolbox adopted by OECD was to base the toolbox on the chemical category concept, which is rooted in chemical similarity. The seminal features of the toolbox are as follows: (1) identify relevant structural characteristics and potential modes of action of a target chemical, (2) identify other chemicals that are similar, especially have the same properties and/or MOA, and (3) use existing experimental data to fill data gaps for untested chemicals.

During his appointment at OECD, Dr. Veith masterfully guided the toolbox through the proof-of-concept phase. After listening to how the OECD member countries use and apply SAR and QSAR models in their assessment of chemicals, he quickly realized that analog identification or category formation, and read-across were at the heart of these activities. Once funding was secured, he worked over the next several years with the toolbox developers and input from the member countries to design a system that meet the needs of the regulatory community and industry. By the release of version 1.0 of the toolbox in 2008, the toolbox had the ability to address many features critical to improved regulatory acceptance of predictive toxicity.

During Dr. Veith's appointment at OECD, his vision of the future and insights into the advanced architecture and workflow of the toolbox were always ahead of current thinking. As the QSAR spotlight shifted to chronic human health endpoints, he was among the first to envision the need for linkages between metabolism and effects models with an understanding of systems biology. As early as 2003, he observed that to meet the challenges of health-related endpoints, scores of chronic toxicity pathways would have to be described.[68] Soon after, he realized that toxicogenomics and other novel methods had the potential to open new doors in clustering chemicals by common toxic pathways for modeling. For example, where metabolic activity is a critical step in the pathway, metabonomics offer unprecedented capacity for identifying key molecular initiating events for chronic effects.

IQF Years

In 2005, Dr. Veith organized the IQF, a volunteer research organization with the aim of advancing alternative methods, especially for human health effects. The IQF focused on the major technical gaps in modeling chronic adverse health effects. Key among the issues he championed via the IQF was the biological response modeling concept known as AOPs. His efforts while at EPA and OECD and with the IQF set the stage for and initiated development of AOPs as a framework to organize existing knowledge associated with the molecular initiating event at the target site, and the cascade of events that result in an adverse response relevant to a particular risk assessment question.[69] He understood that chemicals interfere with normal cellular processes, and that if these perturbations overwhelmed compensatory mechanisms, the result could be injury to cells, tissues, and vital organs. Such injuries eventually are expressed as symptoms and adverse effects in the intact organism. The net result is that the AOP reflects the qualitative and quantitative relationships in the sequence of biological events describing how cellular injuries are propagated as adverse effects to various tissues, organs, and individuals or populations.[59]

As with the fathead minnow database, the AOP approach leverages data in high-quality databases and existing information in the literature to build a WOE to support the final risk assessment. In the process, AOP development helps in the identification of knowledge gaps, weaknesses, and strengths of association along the pathway. Efforts are currently underway[70] to formulate procedures to help in the compilation, organization, and evaluation of the AOP WOE, building on approaches developed for evaluating MOA in human health-risk assessments.[71] Dr. Veith realized that capturing existing information and knowledge about AOPs would be attained through focused workshops of multidisciplinary experts whose initial documentation of current knowledge for specific AOPs could then be expanded through virtual collaboration using the Web.

Starting in 2006, he organized a series of McKim Conferences (named in honor of Dr. James McKim III, a close colleague and collaborator at the EPA laboratory in Duluth, MN). These workshops were held regularly until Dr. Veith's untimely death. While the overarching theme of these workshops was how to use nonanimal data to reduce the need for animal testing, they addressed a variety of topics, including the use of in chemico and *in vitro* data to form chemical categories for read-across and reducing redundancy in assessing cancer (see IQF.com). A seminal effort under the umbrella of the IQF was developing the means to establish a comprehensive AOP database through virtual collaboration. This task was realized through the establishment of Effectopedia, which was one of his many efforts he was actively pursuing when he passed away.

The intended purpose of an AOP is to provide mechanistically plausible, causal linkages between molecular initiating events, *in vitro* results, and human health-related *in vivo* outcomes. Dr. Veith was among the first to realize that the lack of clear intermediate effects for endpoints that can be assessed *in vitro* makes the development and use of AOPs arduous. Among his last scientific endeavors, He worked on how to best use alternative test methods to reduce the need for the long-term rodent carcinogen assay. He fostered a hypothesis-testing framework for organizing short-term evidence. An example of this vision was recently published by Benigni et al.,[72] where rodent carcinogenicity is detected based on the combination of *in vitro* assays and SARs. In this integrated *in vitro*–in silico strategy, genotoxic and nongenotoxic rodent carcinogens are detected with a combination of *in vitro* Ames test, structural alerts for DNA-reactivity carcinogens, and *in vitro* cell transformation assays.

Conclusion

Dr. Veith's vision and leadership during his career provided the scientifically sound technology and understanding needed for regulatory authorities, industry, and the public to employ and accept alternative approaches in testing and evaluating risks of industrial chemicals, pesticides, and pharmaceuticals. His leadership resulted in real-world application of in silico and *in vitro* models in risk assessment methods currently used throughout the world. His many accomplishments were recognized through a number of awards from EPA, including a gold medal, and professional societies, including the 1977 SOCMA Award for Outstanding Achievement in Environmental Chemistry, the International QSAR Award in 1998, and the Henry J. Heimlich, M.D., Award for Innovative Medicine in 2010.

His vision and foresight provided the foundation for the many ongoing national and global efforts to establish a new paradigm of toxicity testing and assessment in the 21st century.[59,60,73] While the technology for chemical evaluation will continue to evolve, the fundamental, hypothesis-based approach that he envisioned transcends time. Developing practical, scientifically rigorous and transparent methods to

evaluate well-defined toxicity endpoints, in the context of MOAs or AOPs, for clearly articulated risk assessment applications in the context of specified regulatory chemical domains is now the foundation of those research efforts that will meaningfully advance 21st-century risk assessments.

The essence of Dr. Veith's approach to advancing alternative methods was first realized in the 1980s with the establishment of the EPA QSAR research program that bridged the new chemicals ''data gap'' under TSCA. The release of the fathead minnow acute toxicity database placed an emphasis on a more mechanistic approach to QSAR model development. OECD subsequently identified the linkage of molecular descriptors used in QSAR models to MOA as one of the five principles for validating QSAR models.[8,9]

As research continues to shift toward testing strategies focused on *in vitro* methods, it will be important to have a clear understanding of how endpoints at lower levels of biological organization relate to the response in the whole organism. In this regard, his efforts while at EPA and OECD and with the IQF set the stage for and initiated development of AOPs as a framework to organize existing knowledge associated with the molecular initiating event at the target site and the cascade of events that result in an adverse response relevant to a particular risk assessment question. His foresight to bring leading experts together through the McKim Conferences to establish a starting point for developing AOPs and capturing additional information as research advances through Effectopedia is now advocated by the OECD and is a major focus of multinational cooperation in supporting integrated approaches to assessment (IATA) and testing.[59]

As with the fathead minnow database, the AOP approach leverages data in high-quality databases and existing information in the literature to build a WOE to support a risk-based evaluation that, depending on the information currently available, can support priority setting, screening, or risk assessment through single-chemical or single-category evaluations. The evolving testing paradigm will require the availability of well-characterized *in vitro* data sets with linkages to relevant adverse outcomes and robust computational models. In the process of developing AOPs, identification of knowledge gaps, weaknesses, and strengths of association along the pathway is required. Development of AOPs provides a knowledge base to inform new research that can be efficiently targeted to advance new IATA applications in drug and pesticide discovery and/or regulatory evaluation efforts. The AOP approach creates a dynamic environment that draws upon an increasingly diverse set of expertise to solve increasingly complex issues, with expertise in systems biology, bioinformatics, omics research, and risk communication, among others, a necessity. The basic principles he used in leading the development and availability of QSAR models and associated toxicity knowledge bases will help ensure establishment of efficient and relevant research and risk assessment methods that are increasingly based on the use of *in vitro* assays and data.

Dr. Veith's efforts while at EPA and OECD, and through his leadership of the IQF, with his continued efforts to establish an AOP knowledge base, taken together, represent a prodigious body of work and accomplishment. The continued advancement of alternative methods for chemical testing and evaluation will be founded on the principles and foresight he established over his four decades in designing and implementing research focused on real-world applications. Beyond the ''scientific'' leadership he provided, with the many breakthroughs attained, perhaps his ability to create productive, diverse teams of free-thinking scientists committed to public service above all else may be his greatest achievement. Our collective commitment to foster and emulate his ability to bring together dedicated teams of researchers, risk assessors, and risk managers to pursue and realize goals larger than anything we could accomplish alone will be our best way to honor Dr. Veith's legacy.

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Author Disclosure Statement

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