Wendy Warr Interviews Han van de Waterbeemd

Han van de Waterbeemd studied physical organic chemistry at the Technical University of Eindhoven, The Netherlands, and did a Ph.D. in medicinal chemistry at the University of Leiden, The Netherlands. After a postdoc with Bernard Testa at the School of Pharmacy of the University of Lausanne, Switzerland, he held a 5-year faculty position at the same institution. He has also taught medicinal chemistry to pharmacy students at the universities of Berne and Basel in Switzerland from 1987-1997. In 1988 he joined F. Hoffmann-La Roche Ltd in Basel as head of the Molecular Properties Group. He moved in 1997 to Pfizer Central Research UK, later Pfizer Global Research and Development and held various positions in the Department of Drug Metabolism, later called PDM (Pharmacokinetics, Dynamics and Metabolism), including head of discovery, and head of automation and *in silico* ADME technologies. In 2005 he moved to AstraZeneca to become global project leader of C-Lab, their molecular properties and *in silico* ADMET modeling platform. He has published more than 135 peer reviewed papers and book chapters, and (co-)edited 11 books. His research interests include physicochemical and structural molecular properties and their role in drug disposition, as well as the *in silico* modeling of ADMET properties. Han was secretary of the QSAR and Modeling Society 1995-2005. Hobbies include various sports such as running, mountain biking, hiking, skiing, badminton, tennis. Further interests include Mediterranean gardening and wine tasting.

Recent Books

ADME/Tox Approaches; Testa, B.; van de Waterbeemd, H., Eds. In *Comprehensive Medicinal Chemistry*, 2nd ed.; Taylor, J. B., Triggle. D. J., Eds.; Elsevier: Oxford, England 2007; Volume 5.

Pharmacokinetics and Metabolism in Drug Design, 2nd ed.; Smith, D.A.; van de Waterbeemd, H.; Walker, D. K., Eds.; Wiley-VCH: Weinheim, Germany, 2006**.**

van de Waterbeemd, H.; Rose, S. Quantitative approaches to structure-activity relationships. In Part IV. Substituents and Functions: Qualitative and Quantitative Aspects of Structure-Activity Relationships, *The Practice of Medicinal Chemistry*, 2nd ed.; Wermuth, C., Ed.; Academic Press: Amsterdam, The Netherlands, 2003; pp 351-369. (Third edition is currently in preparation.)

Drug Bioavailability: Estimation of Solubility, Permeability, Absorption and Bioavailability; van de Waterbeemd, H.; Hans Lennernäs, H.; Per Artursson, P. Eds.;

Wiley-VCH: Weinheim, Germany, 2003. (Second edition is currently being prepared by Han van de Waterbeemd and Bernard Testa.)

Interview

Dr. Warr: I couldn't find a biography for you on the Web. Do you have a personal home page?

Dr. van de Waterbeemd: I don't have one since I've worked in the pharmaceutical industry since 1988 and didn't want to compromise myself too much. Being active in the field gives enough exposure. A Google search on "Van de Waterbeemd" gives 51,400 hits, while Yahoo produces 10,700.

WW: What led you into the QSAR and ADMET fields?

HvdW: I started with QSAR during my PhD thesis (1977-1980) at the University of Leiden. We tried to see whether rate constants of partitioning could be more useful than partition or distribution coefficients. Many of us realized much later the relevance of this work in relation to membrane transport. Compare, for example, log *P* octanol/water with log *Papp* in Caco-2 or PAMPA measurements, or equilibrium constant *versus* rate constant.

I grew in the ADMET field during my career path at Pfizer (1997-2005) where I worked in the DMPK department. Initially I was a DMPK drug discovery manager, but gradually went to a role in automation of *in vitro* measurements and *in silico* prediction of ADME properties.

WW: Has anyone been your inspiration, personally?

HvdW: Probably two names stand out. I met Hugo Kubinyi during my PhD and we still are good friends. Then I did my post doc with Bernard Testa in Lausanne and worked in his lab for 8 years. We still work together on book-editing projects e.g., ADME-Tox Approaches in *Comprehensive Medicinal Chemistry,* the bible in the field! I also thank John Dearden for running a number of miles together.

WW: The van de Waterbeemd data set was first published in 1987. Is it still used? Are disjoint principal properties (DPPs) still used as descriptors?

HvdW: I forgot about this! You probably refer to the substituent values we collected and analyzed. We showed that lipophilicity could be seen as composed of a size (volume) and a polarity (H-bonding) term. This is a very useful insight for the medicinal chemist. DPP was a concept developed by Sergio Clementi, but it never took off.

WW: A recent paper of yours recommends using more current data for making predictions and suggests a need for auto-updating QSAR models.

HvdW: There is very little literature on the behavior of QSAR models over time. At AstraZeneca we are doing some systematic investigations on this (Rodgers, S. L.; Davis, A. M.; van de Waterbeemd, H. Time-Series QSAR Analysis of Human Plasma Protein Binding Data *QSAR & Combinatorial Science* 2007, *26*(4), 511-521). Over time, projects move away in chemical space from the original training set and so the models age and predictions get worse. We therefore need ways of rebuilding the models automatically to make maximum use of more recent experimental measurements. We, and others are working on this.

WW: I see that you are an IUPAC Fellow. I assume, therefore, that you have made significant contributions to IUPAC.

HvdW: I am a co-author of the glossary of terms used in computational drug design **<**http://www.iupac.org/publications/pac/1997/pdf/6905x1137.pdf**>.** I also contributed to the glossary of terms in medicinal chemistry http://www.iupac.org/reports/1998/7005wermuth/index.html, in a team led by Camille Wermuth.

WW: You have also been involved in the QSAR and Modeling Society, the UK QSAR and ChemoInformatics Group, the Society of Chemical Industry and other organizations. In which societies are you now most active?

HvdW: I also enjoyed conference organization and was involved in the European QSAR meetings in Interlaken, Strasbourg, Lausanne (as chair), and Bournemouth. My other interest is physicochemical properties and with Bernard Testa, I set up a series of "logP" meetings starting in 1995 with the next planned "logP2009" to be held in Zürich. I also co-organized meetings around lead profiling, for the European Federation for Pharmaceutical Sciences (EUFEPS) in collaboration with the American Association of Pharmaceutical Scientists (AAPS). I have put my society work on hold to concentrate fully on book editing.

WW: You have written quite a few books and book chapters. How do you find the time for this sort of prodigious effort?

HvdW: For book editing you need to be very organized, have many good friends, and some idea of what you want. I also believe that in many cases it makes sense to work with co-editors to have a wider coverage of science and more dialog about the manuscripts. I find time by combining editing with sports and other relaxations. I can easily work (edit!) in the garden in the sun. It all comes down to using your time efficiently and enjoying it.

WW: **I gather that you are in the process of updating your section for the third edition of *The Practice of Medicinal Chemistry*. What has changed?**

HvdW: This will be again in collaboration with Sally Rose (a former chair of the UK QSAR Group, working with a former secretary of the QSAR and Modeling Society!). Initially I thought this would be a simple update. However, it soon became clear that

much has changed. New methods such as SVM have arrived. Typical, also, is the construction of consensus models. New statistics include the use of a confusion matrix and ROC curves. We also will expand the section on model building and validation. There will be some thoughts on autoQSAR, inverse QSAR, and lazy QSAR. The field is moving! And that in times where some of our colleagues think that chemoinformatics is all that matters!

WW: A SciFinder search for your name produces more than 160 references since 1980. That is a very high number for a scientist in industry. Have you ever been tempted to move into academia?

HvdW: Yes, I have, but it did not happen. During my industrial years I have kept an interest in academia and I have been involved in teaching at various universities and courses. In particular, in 1994, for the Swiss Medicinal Chemistry Society, I set up the 2-yearly Swiss Course on Medicinal Chemistry held in Leysin in the beautiful Alps.

WW: Anything else we should know about?

HvdW: I am proud to be the inventor of polar surface area (PSA) as a descriptor (van de Waterbeemd, H.; Kansy, M. *Chimia* **1992**, *46*, 299-303). We wanted a simple measure for hydrogen bonding capacity and wanted to avoid tedious measurements. This is where I made the step from *in vitro* to *in silico*. Today we use the hybrid approach, called *in combo*, to get the best predictive results. This is an example of my philosophy, try easy things and do not always try to be over-sophisticated. Having said that, much academic research is sometimes needed to come to such a simple conclusion!

WW: What would be your advice to anyone embarking on career in QSAR nowadays?

HvdW: Try to get a picture of QSAR history and its heroes. I see many youngsters reinventing the wheel, while they would do better to buy and read some good books written or edited by enthusiasts like myself.