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DEVELOPMENT OF METHODS AND TECHNOLOGIES OF INFORMATICS FOR PROCESS MODELING AND MANAGEMENT

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This book consists of papers describing applications of informatics in process modeling and management and in environmental engineering. Problems presented in the papers concern development of methods supporting process management, development of calculation methods for process modeling and development of technologies of informatics for solving some problems of environmental engineering. In several papers results of the research projects supported by the Polish Ministry of Science and Higher Education are presented.

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CHAPTER 3

Tools of informatics in environmental engineering

METHOD OF EVALUATION BY ORDER THEORY APPLIED ON THE ENVIRONMENTAL TOPIC OF DATA-AVAILABILITY OF PHARMACEUTICALLY ACTIVE SUBSTANCES

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Abstract: *Reports on pharmaceuticals and personal care products (PPCPs) have raised substantial concern in the public concerning drinking water and reclaimed wastewater quality issues. Targeted ecotoxicological studies are lacking almost entirely and such investigations are needed focusing on subtle environmental effects. This will allow better and comprehensive risk assessments of pharmaceuticals in the future (Fent et al., 2006).*
In our last year's contribution to the conference "Applications of Informatics in Environment Engineering and Medicine" (Voigt et al., 2005a) we presented the results of an intensive literature study on selected pharmaceuticals which were detected in the water environment. As concluded in the study the data availability on pharmaceuticals should be scrutinized. Hence follows the urgent need for evaluation of the data-availability on pharmaceuticals in environmental and chemical databases. A data-matrix consisting of 22 databases and 16 pharmaceuticals is set-up.
The consideration of the chosen pharmaceutical in databases x is coded 0 = not available, or 1 = available. The mathematical evaluation method applied in this approach is named METEOR (Method of Evaluation by Order Theory) and has its origin in discrete mathematics. METEOR is used for aggregation and weighting procedures of data-matrices. The basic idea is that subsets of the information base IB can be combined by weighted sums, where the weights are the components of the tuple g. Several logical aggregations of pharmaceuticals will be demonstrated. All approaches show that the data-situation on the chosen test-set of 16 well-known and high produced pharmaceuticals is far from being satisfactory. The issuse of pharmaceuticals in the environment and the unavailability of data necessitate much closer communication between science and medical healthcare and politicians.

Keywords: Hasse Diagram Technique, METEOR, ranking, multi-criteria decision support, environmetrics, chemometrics, environmental chemicals, pharmaceuticals in the environment, environmental pollution.

1. Introduction Pharmaceuticals in the Environment

Estimations are performed which say there may be as many as 6 million pharmaceuticals and personal care products (PPCPs) commercially available worldwide and that the use of pharmaceuticals is increasing 3-4% by weight per annum (Daughton, 2004). It is estimated that Germany also uses over 600 tonnes per year of antibiotics with some 300 tonnes per year used in France, Italy and Spain. Over 3000 active substances are licensed for use within the UK with paracetamol (2000 tonnes per year), acetylsalicylic acid (770 tonnes per year) and metformin (106 tonnes per year) being the highest usage drugs. A total of 170 pharmaceutical chemicals are estimated to be used in excess of tonnes per year. With increasing urbanization and associated commercial activities, and an increasing concern with personal care and health, the significance of PPCPs as a societal lifestyle cause of water pollution is likely to impose an increased risk (Ellis, 2006). The elimination of emerging contaminants such as pharmaceuticals and personal care products in waste water treatment plants (WWTPs) applying conventional activated sludge treatment (AST) and advanced treatment processes, such as membrane bioreactors (MBRs) and advanced oxidation processes (AOPs), as well as during production of drinking water is studied by several authors (Petrovic et al., 2003), (Yoon et al., 2006). Studies of the ecological risk of pharmaceuticals are very few as revealed in a review paper by Fent et al. (2006). A lack of ecotoxicoliogical and fate data on pharmaceuticals is evident. The extent to which data is missing should therefore be looked upon in more detail in order to trigger further political steps in performing studies concerning the risk assessment of pharmaceuticals in the environment. Several evaluation procedures of the data-availability on pharmaceuticals as welll as on high-production volume chemicals have been performed and published (Voigt and Brüggemann, 2005b), (Voigt et al., 2006).

In the present paper we enhanced not only the number of pharmaceuticals adding point-source pharmaceuticals like cytostatic agents and contrast media, but also the number of Internet databases to be evaluated. Concerning the environmetrical evaluation method we put the emphasis on the aggregation and weighting of attributes outlined under the term Method of Evaluation by Order Theory (METEOR).

2. METEOR (Method of Evaluation by Order Theory)

2.1. Background and software

The basis of the Hasse Diagram technique (named HDT for short) is the assumption that a ranking can be performed while avoiding the use of an ordering index (Halfon, Reggiani, 1986). For an evaluation of the objects they must be compared. The comparison is done by examining characteristic properties (attributes, descriptors) of these objects. If the evaluation is aimed to assess criteria, then the attributes or (synonyms: descriptors) are thought of as measures, how well a crite-

rion is fulfilled. Attributes are -in the case of the object "x" denoted as $q(1,x)$, $q(2,x),...,q(m,x)$ and often written as a tuple $\boldsymbol{q}(x)$. We avoid the term vector, because the properties of a linear space are not needed in the HDT. Often the properties are gathered to a set without reference to actual values realized by the objects. This set of properties is called an information base IB. Often subsets of IB are needed.

The Hasse Diagram Technique is well explained in a variety of different environmental and chemical as well as statistical journals. A rather comprehensive description can be found in (Brüggemann, Welzl, 2002). A comparison of the Hasse Diagram Technique with multi-variate statistical methods is given by Voigt et al. (2004a,b). Therefore only some aspects are picked out, which will be useful in the subsequent application. Hasse Diagrams visualize the order relations within objects: Two objects, also called elements (if the aspect of belonging to sets is important) x, y of an object set are considered as being ordered, e.g. $x \leq y$, if all scores of x are less or equal than those of y. Hasse Diagrams are acyclic digraphs and objects are drawn as small circles together with an appropriate identifier. The edges of this graph are the cover-relations; that means, edges which express simply the transitivity are omitted, as they bear redundant information. In our applications the circles near the top of the page (of the Hasse Diagram) indicate objects that are the "better" objects according to the criteria used to rank them: The objects not "covered" by other objects are called maximal objects. Objects which do not cover other objects are called minimal objects. In some diagrams there exist also isolated objects which can be considered as maximal and minimal objects at the same time. Sometimes it is useful to call those elements as 'proper', which are not at the same time both, maximal and minimal elements.

The WHasse program is developed, improved and updated by Rainer Brüggemann (a brief technical information about the WHasse-program, written in DELPHI, can be found in a publication from the second author (Brüggemann et al., 1999a) and is available for non-commercial use from the second author. The mathematical basis is described in Brüggemann et al. (2001a). The commercial software is called ProRank Software for multi-criteria evaluation and decision support. For commercial applications it is recommended to contact the company Criterion – Evaluation and Information Management (Criterion, 2006).

2.2. Aggregation and weighting

Aggregation procedures of the data-matrix will be performed by applying METEOR (Method of Evaluation by Order Theory). The basic idea is that subsets of IB can be combined by weighted sums; see Brüggemann et al. (Brüggemann, 2001b). Therefore the columns of the data-matrix (rows: the elements, columns the attributes) must be considered as vectors of a linear space. In order to combine them freely, a common scaling level must be assumed. Formally an embedding onto an appropriate metric space must be performed, which -however- needs a careful analysis of the scale level of the attributes. Each positive monotonous combination of -

say- two attributes, leading to a "superattribute" corresponds order theoretically to an order preserving map. One may see this as "climbing up" a hierarchy of criteria: Basically a very detailed study is possible by means of a large set of indicators. Often indicators can be grouped as for example toxicities of different species may be aggregated to an ecotoxic potential. This conceptual grouping has its counterpart by numerical aggregation of indicators. Here the weighted sum is selected as aggregation procedure. Usually the aggregation is done step by step, therefore the role of weighting can be traced back, when the final result, a linear order is obtained. Furthermore, checking the local incomparability of any element $x \in E/R$, i.e.

$$U(x) := \text{card}\ \{y: y \parallel x\ , y,x \in E/R\}$$

it is possible to identify weight-sensible and weight-insensible elements of the ground set E and E/R, resp., see Brüggemann et al. (Brüggemann, 2001a). If the attributes of a set of objects are considered as entries of a data-matrix then it might be useful to briefly discuss possible aggregations (often just linear combinations) of the entries $q(x,j)$ of the matrix.

There are three possibilities, which are discussed in Table 1:

Table 1. Combination of the Entries of the Data-matrix.

$\lambda_{j1} \cdot q(x,j_1)+\lambda_{j2} \cdot q(x,j2)+...$	Combination of attributes	METEOR, hierarchy of indicators, different scale level might be combined
$\mu_x \cdot q(x,j)+\mu_y \cdot q(y,j)+...$	Combination of objects, leading for example to "pseudo-objects"	PREPROCESSING, for example by object reduction processes. For example classification as discussed by Brüggemann, Bartel, 1999b Not needed in many applications of HDT
$f(q(x,j_1),q(x,j_2),q(y,j_1),q(y,j_2))$	Combination of both	PREPROCESSING, for example Cluster analysis based on distances, see for example Luther et al., 2000

q = attribute or indicator, x,y = objects, j_1,j_2 = indicate specific indicators or attributes of IB, μ,λ = scalars

An example of the application of METEOR on the evaluation of literature on pharmaceuticals is given by the first author (Voigt and Brüggemann, 2005b).

2.3. W-matrix: Dissimilarity-matrix

The W-matrix describes the influence of the attributes on the Hasse Diagram. The entries of the W-matrix are a measure for the metric distance among posets,

based on the same ground set of objects, but induced by different subsets of IB of m-1 attributes, i.e. subset generated by IB – $\{q_i\}$, i= 1,..., m. The definitions of the entries of the W-matrix depend on the actual selected subset of elements of E. Mostly the full ground set E is used. For further reading we refer to background publications by Brüggemann and Welzl (2002) and Brüggemann et al. (1999a).

3. Evaluation of 22 Databases with repect to 16 Pharmaceuticals

3.1. Set-up of Data-matrix (22 objects x 16 attributes)

We set-up a set of objects comprising 22 Intenet databases (see Table 2) and an information base of 16 pharmaceuticals (Table 3).

Table 2. List of 22 Internet Databases (Objects).

No	Name	Abb.	URL
1	Biocatalysis/Biodegradation Database	BID	http://umbbd.ahc.umn.edu/
2	Chemicals Information System for Consumer-relevant Substances (CIVS)	CIV	http://bfr.zadi.de/civs/
3	ChemExper Catalog of Chemical Suppliers, Physical Characteristics	CEX	http://www.chemexper.com/
4	Chemfinder	CHF	http://chemfinder.cambridgesoft.com/
5	ECOTOX	ECO	http://www.epa.gov/ecotox/
6	Envirofacts	ENV	http://www.epa.gov/enviro/html/emci/chemref/index.html
7	Environmental Fate Database	EFD	http://www.syrres.com/esc/efdb.htm
8	Environmental Health Criteria Monographs (EHCs)	EHC	http://www.inchem.org/pages/ehc.html
9	ESIS – European Chemical Substances Information System	ESI	http://ecb.jrc.it/esis/
10	EXTOXNET	EXT	http://extoxnet.orst.edu/tibs/ghindex.html
11	GESTIS – Dangerous Substances Database	GES	http://www.hvbg.de/d/bia/fac/stoffdb/index.html
12	GSBL Public	GSB	http://www.gsbl.de
13	HSDB	HSD	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
14	IARC	IAR	http://www-cie.iarc.fr/htdig/search.html
15	International Chemical Safety Cards	ICS	http://www.ilo.org/public/english/protection/safework/cis/products/icsc/
16	INTOX	INT	http://www.intox.org/databank/index.htm
17	N-Class Database	NCL	http://www.kemi.se/nclass/default.asp
18	Oekopro	OEK	http://www.oekopro.de/?s=1005&l=EN
19	OECD Integrated HPV Database	OIH	http://cs3-hq.oecd.org/scripts/hpv/
20	RXList The International Drug Index	RXL	http://www.rxlist.com/
21	SIRI MSDS	SIR	http://hazard.com/msds/index.php
22	SRC PhysProp Database	SRC	http://www.syrres.com/esc/physdemo.htm

These 22 databases can be catagorized into four different types of numerical databases can be distinguished:

- Single databases which cover only one data collection (BID, CIV, GES, GSB, HSD, IAR, ICS, NCL, OEK, SRC)
- Multi-database databases which encompass several databases under the same name and search interface (ECO, ENV, EFD, ESI, EXT, INT)
- Monograph databases which cover extensive reviews on very few chemicals (EHC, OIH)
- Catalogue database (CEX, CHF, RXL, SIR).

The given abbreviations are important for the further evaluation procedure.

The consideration of the following pharmaceuticals is found in the database x is coded by 0 = not available, or 1 = available.

Table 3 gives the list of pharmaceuticals with their CAS-numbers and abbreviations. In row three the drug groups are indicated. The chosen pharmaceuticals belong to nine different drug groups: Analgesics (ANAL), antibiotics (ANTI), antiepileptics (AEPI), beta blocker (BETA), contrast media (CONT), cytostatic agents (CYTO), lipid regulators (LIPI), phychiatric drugs (PHYS) and steroids (STER).

Table 3. List of 16 Pharmaceuticals (Criteria).

Name of Drug	ACR.	Drug group	CAS-Number
Bezafibrate	BEZ	Lipid regulator	41859-67-0
Carbamazepine	CAR	Antiepileptic drugs	298-46-4
Clofibric acid	CLO	Lipid regulator	882-09-7
Cyclophoshamide	CYC	Cytostatic agent	6055-19-2
Diazepam	DAP	Psychiatric drug	439-14-5
Diclofenac	DIC	Analgesic	15307-86-5
Diatrizoate	DIT	Contrast Media	117-96-4
Ethinyl Estradiol	EES	Sex hormones, Steroid	57-63-6
Fenofibrate	FEN	Lipid regulator	49562-28-9
5-Fluorouracil	FLU	Cytostatic agent	51-21-8
Ibuprofen	IBU	Analgesic	15687-27-1
Iopromide	IOP	Contrast Media	73334-07-3
Metoprolol	MET	Beta blocker	37350-58-6
Phenazone	PHE	Analgesic	60-80-0
Roxithomycin	ROX	Antibiotic	80214-83-1
Sulfamethoxazole	SUL	Antibiotic	723-46-6

3.2. Outline of Evaluation Procedure

The evaluation of the 22 Internet databases by pharmaceuticals will be conducted in a step-wise approach. First we evaluate the complete data-matrix (22x16)

by drawing a Hasse Diagram (Figure 2). Then we determine the influence of the criteria on the ranking and find out which criterion is the most important one. This criterion will be left out and the Hasse Diagram for the reduced data-matrix (22x15) will be presented (Figure 3). In a further step the attributes will be combined according to the nine groups of pharmaceuticals introduced in Table 3. This procedure leads to a 22x9 data-matrix (Figure 4). In the final evaluation step we weight the contrast media twice as high as the rest of the pharmaceuticals. This induces a 22x2 data-matrix (Figure 5). The evaluation steps are outlined in Figure 1 for a better understanding.

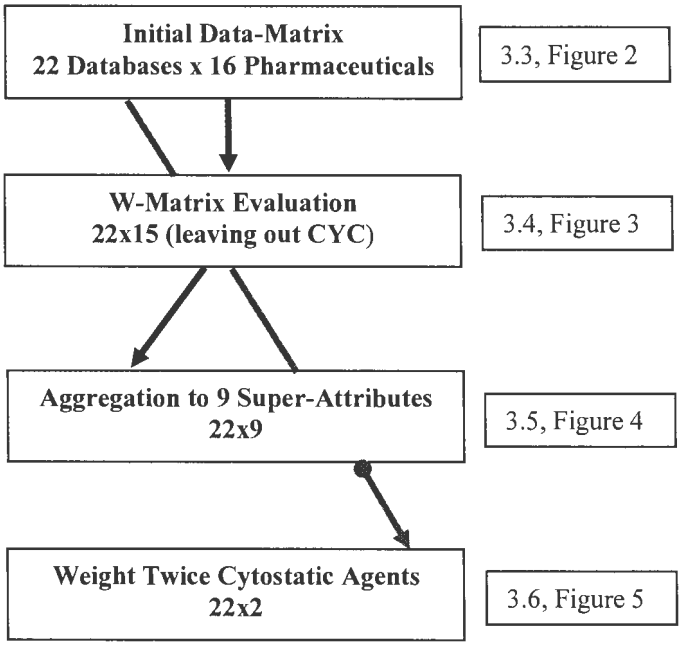
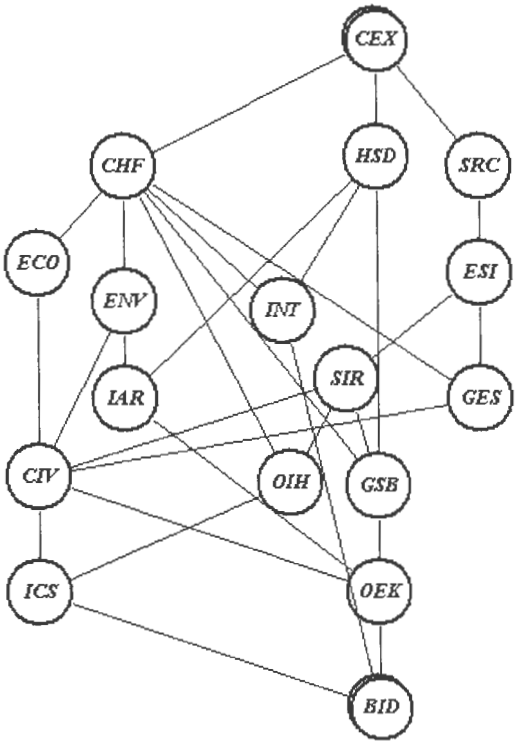


Figure 1. Evaluation Steps.

By applying aggregation and weighting procedures we introduce the possibility of decision-making and expert judgement into the initially purely objective and mathematically-driven methodology of partially ordered sets.

3.3. Evaluation by Hasse Diagram Technique (Complete Data-matrix)

In the first evaluation step we compute the Hasse Diagram of the complete 22x16 data-matrix. The result is given in Figure 2.



equivalent objects: {CEX;RXL}, {BID;EFD;EHC;EXT;NCL}

Figure 2. Hasse Diagram of 22 Databases evaluated by 16 Pharmaceuticals.

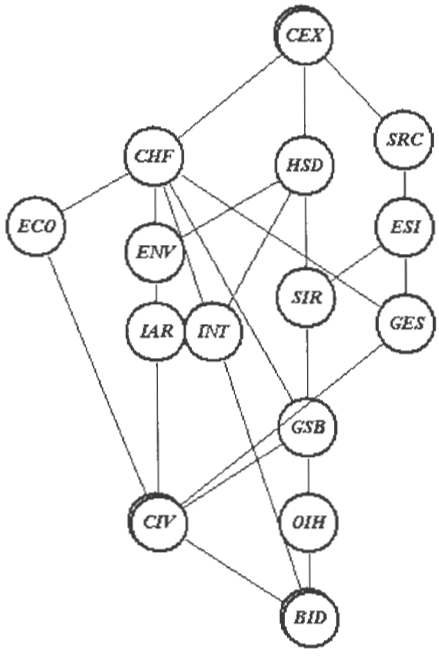
The Hasse Diagram in Figure 2 is structured into seven levels. The objects BID and CEX have a stronger circle which means they are equivalent objects. The maximal object is CEX, the minimal object BID. Considered as representatives of the classes of the quotient set under the equivalence relation "equality" BID and CEX are least and greatest elements. Taking a look at all objects (quotient set) 112 incomparabilities, 80 comparabilities are counted, and this means that there are more incomparabilities than comparabilities.

Although some important ranking information can be drawn out of the diagram, the figure calls for further data-analysis steps in order to draw more comprehensive conclusions from the data-matrix. In this paper we follow the methodologies which comprise partial order tools to aggregate and weight attributes.

3.4. Study of the Influence of Attributes: W-Matrix

The W-matrix is calculated for all objects. The results reveal that the omission of Phenazone (PHE) and the two cytostatic agents Cyclophosphamide (CYC)

and 5-Fluorouracil (FLU) have the greatest impact on the Hasse Diagram. As an example the Hasse Diagram of case 14 (omission of PHE) is presented in Figure 3.



Equivalent Objects: {BID;EFD;EHC;EXT;ICS;NCL} {CIV;OEK} {CEX;RXL}

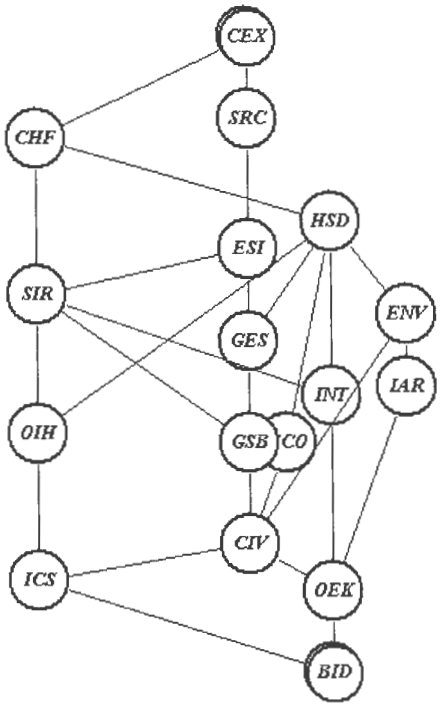
Figure 3. Hasse Diagram of Case 14 (Attribute PHE left out): 22x15 Data-Matrix.

Figure 3 shows immediately visible changes to the original Hasse Diagram presented in Figure 2. First it is shown that the number of incomparabilities diminished whereas the number of comparabilities increased. The equivalence class CEX, RXL is still the maximal object. Concerning the equivalence class which forms the minimal object the databases ICS joined now. A new equivalence class is given by the objects CIV, OEK. This initial step leaving out one important attribute leads to significant changes in the diagram and in the results of the data-analysis.

3.5. Aggregation of Attributes to Nine Super-Attributes

As outlined in section 3.1 the pharmaceuticals belong to nine different groups according to their use and effects. Hence it follows that we aggregate the pharmaceuticals belonging to one group, e.g. cytostatic agents Cyclophosphamide (CYC) and 5-Fluorouracil (FLU) to the group CYTO. There are drug groups which com-

prise one, two or three pharmaceuticals. After performing this aggregation procedure we draw the Hasse Diagram of the 22x9 data-matrix as demonstated in Figure 4.



equivalent objects: {BID;EFD;EHC;EXT;NCL} {CEX;RXL}

Figure 4. Hasse Diagram of 9 Super-Indicators (22x9 Data-matrix).

The greatest and least representatives remain the same as in the original Hasse Diagram of Figure 2 as it must be considered the fact of aggregation as an order preserving map. The number of levels has increased from 7 in the diagram of the comple 22x16 data-matrix to 8 in the 22x9 data-matrix. As an example the pair HSD, CHF may be considered: In Figure 3 HSD is incomparable with CHF whereas in Figure 4 CHF is dominating HSD. However, one can conclude that the aggregation step does not have a huge impact on the structure of the diagram. Hence one can not draw a lot more conclusions out of this data-analysis step.

The next step of weighting attributes will have a greater impact on the structure of the Hasse Diagram as it puts a subjective instrument into the ranking procedure.

3.5. Aggregation of Attributes to Two Drug Groups

As outlined before the cytostatic agents have a great impact on the ranking (see section 3.3). In most cases these pharmaceuticals are found in the effluents of hospitals. One might therefore postulate that one is more interested in the impact of those two chemicals Cyclophosphamide (CYC) and 5-Fluorouracil (FLU) than on the rest of the chemicals.

Let n_1 and n_2 be the numbers of attributes in two attribute groups (here: cytostatic agents (2), other pharmaceuticals (14))

w_1 and w_2 the weights by which the attributes of the one group and those of the other group are combined

m the relative weight (e.g. 2)

Then, maintaining the normalization to 1 the weights can be calculated as follows:

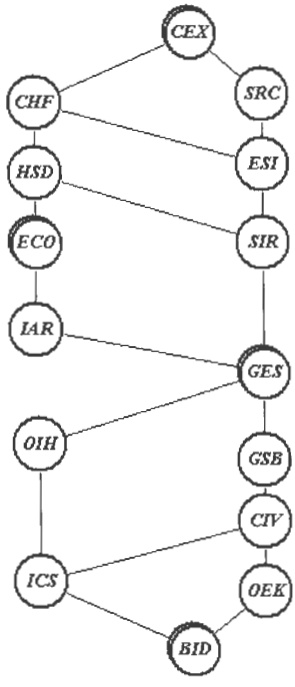
$$w_2 = w_2 \frac{1}{(n_1 \cdot m) + n_2} \tag{1}$$

$$w_1 = m \cdot w_2 \tag{2}$$

It is easily shown that

$$1 = \sum_{i=1}^{n1} w_1 + \sum_{i=1}^{n2} w_2 \tag{3}$$

Applying this procedure to given data-matrix weighting the cytostatic agents twice with repect to all the 14 other chemicals we receive the Hasse Diagram presented in Figure 5. This diagram shows great difference to the original diagram of Figure 2. The aggregation and weighting has of course an enormous impact on the structure of the diagram. The number of levels increased from 7 to 9. The Hasse Diagram in Figure 5 shows many more comparabilities than incomparabilities. However in the extreme objects, say the minimal and maximal objects remain the same. It should be pointed out that the equivalent objects GES=INT has a special position in the Hasse diagram. This equivalence class is a so-called articulation point. If we leave out this object than the Hasse Diagram is separated into two parts. For further explanations we refer to the publication by Voigt et al. (2004b).



equivalent objects: {BID;EFD;EHC;EXT;NCL} {CEX;RXL} {ECO;ENV} {GES;INT}

Figure 5. Hasse Diagram of Weighting Cytostatic Agents Twice as Important as the Rest of the Pharmaceuticals (22x2 Data-matrix).

4. Discussion and Conclusions

In the present paper the subject of the occurrence of pharmaceuticals in numerical Internet databases is envisaged. Targeted ecotoxicolgical studies are lacking almost entirely and many investigations are needed focusing on subtle environmental effects of pharmaceuticals (Fent et al., 2006). Environmetrical and chemometrical studies on the availability of data on pharmaceuticals should support the need for more research on the topic of pharmaceuticals in the environment.

The results of this paper demonstrate again that the lack of data on pharmaceuticals is evident. We evaluated 22 well-known databases in the field of environmental chemicals and found out that five databases BID;EFD;EHC;EXT;NCL do not give any data on the chosen 16 pharmaceuticals detected in the water environment. These are databases which focus environmentally-relevant data on chemical substances. On the other hand only two catalogues databases namely CEX (ChemExper Catalog of Chemical Suppliers, Physical Characteristics) and RXL (RXList the International Drug Index) have data on all pharmaceuticals. These two catalogue databases comprise only basic identification parameters on the chemicals as well as

some physical chemical properties and the use and effect on humans. No environmental data such as degradation, accumulation and ecotoxicological data are given in these databases.

Concerning the application of METEOR-Method of Evaluation by Order Theory aggregation and weighting procedures are introduced. They reveal significant differences in the resulting Hasse Diagrams. However no changes take place in the positioning of the discussed extreme objects; say the minimal and maximal objects remain the same.

Aggregation and weighting provide the possibility of introducing expert knowledge or decision making arguments into the evaluation method. We will continue our scientific work in studying the influence of aggregation and weights on the structure of the Hasse Diagrams. With respect to the topic of pharmaceuticals in the environment we will pursue our investigation concerning the contents of the databases.

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DEVELOPMENT OF METHODS AND TECHNOLOGIES OF INFORMATICS FOR PROCESS MODELING AND MANAGEMENT

The purpose of this publication is to popularize application of informatics in process modeling and management and in environmental engineering. The papers published are thematically selected from the works presented during the conference '*Multi-accessible Computer Systems*' organized by the Systems Research Institute and the University of Technology and Agriculture in Bydgoszcz for several years already in Ciechocinek. Problems presented in the papers concern: development of quality and quantity methods supporting the process management, development of quantity methods for process modeling and simulation, development of technologies of informatics for solving problems of environmental engineering. In several papers results of research projects supported by the Polish Ministry of Science and Higher Education are presented.

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