CONTRAST AGENTS - IODINATED PRODUCTS. SECOND WHO-ITA / ITA-OMS 2010 CONTRIBUTION ON AGGREGATE WHO SYSTEM-ORGAN CLASS DISORDERS AND/OR CLUSTERING BASED ON REPORTED ADVERSE REACTIONS/EVENTS

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Summary

From the 2010 total basic adverse reactions and events collected as ADRs preferred names in the WHO-Uppsala Drug Monitoring Programme, subdivided in its first two twenty years periods as for the first seven iodinated products diagnostic contrast agents amidotrizoate, iodamide, iotalamate, iodoxamate, ioxaglate, iohexsol and iopamidol, their 30 WHO-system organ class disorders (SOCDs) aggregates had been compared. Their common maximum 97% levels identified six SOCDs only, apt to evaluate the most frequent single ADRs for each class, and their percentual normalization profiles for each product.

The WILKS's chi square statistics for the related contingency tables, and Gabriel's STP procedure applied to the extracted double data sets then produced profile binary clustering, as well as Euclidean confirmatory plots. They finally showed similar objectively evaluated autoclassificative trends of these products, which do not completely correspond to their actual ATC V08A A, B and C subdivision: while amidotrizoate and iotalamate, and respectively iohesol and iopamidol are confirmed to belong to the A and B subgroups, ioxaglate behaves fluctuating within A, B and C, but iodamide looks surprizingly, constantly positioned together with iodoxamate as binary/ternary C associated. In view of the recent work of Campillos et al (Science, 2008) which throws light on the subject, the above discrepancies do not appear anymore unexpected or alarming. They found indeed, that similarity of ADRs profile does not presuppose similarity of drug composition.

Our pilot study is to be extended to all the products in use today globally, for the same iodinated RX contrast media as well as for the NMR imaging contrast agents. What we might finally get evaluated, together with the mostly economical associated burden, would be their most appropriate, beneficial diagnostic chemotoxicity control. The aim is to sustain the continuous needed process of standardization & development of the still unique most internationally comprehensive WHO-sponsored drug monitoring project, which, starting in the field, should lead to better unbiased values and more complying iterative protocols.

Key words: WHO-Uppsala iodinated contrast products monitoring; WILKS's chi square statistics for contingency tables; Gabriel's STP procedure; binary clustering; comparisons of WHO-System Organ Class Disorders and/or ADRs and events collected over the first 20 years of monitoring with reference to amidotrizoate, iodamide, iotalamate, iodoxamate, ioxaglate, iohexol, and iopamidol (preferred names).

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Various methods have been applied to the study of medicinal products to gain more detailed information (for instance a group of cholinergic drug variants have been subjected to a battery of pharmacometric tests to achieve an objective definition of receptor subclasses [1]); these methods have ranged from the automatization of analytical assays (Cf [2]) to the classification reconstruction of the dynamics (and kinetics) of their effects also in humans (e.g. [3]). After working on their development and experimental application, also using other approaches [4], and after participating in the foundation of the international feedback collection system, in 1989-90 we published a first paper on the human use of radiological iodinated contrast agents, which unlike therapeutic products should not ideally produce, but in fact do give rise to, side effects diagnosed and/or observed as adverse effects and/or events, which then are duly reported to the international collecting body as adverse reactions (ADRs). These have largely been standardized, beginning with the use of "preferred terms" and codes, and subsequently systematically aggregated into 30 system-organ class disorders (SOCDs) [5, 6]. The first national paper, updated to July 2010, has recently been submitted with the Editor's authorization to this online journal of the Italian Society of Pharmacology (SIF)[5]. It is limited to the same seven products (aggregated as acids and salts) of the updated ATC 2010 classification of products V08A A, B and C (see their current complete list in [(1)], p 23) and reports the number of ADRs they have totalled from the beginning of the monitoring system, in 1968, to 1989. Here we make reference not only to those of the first two decades, but also to the data of the 3rd and 4th decade (1990-2010), grouped first into the same number of the same SOCDs (as indicated in the legend to Fig. 1), applying to them for the first time in the current context of WILKS' chi square statistics, as reported below in section 2. The method will subsequently be applied to all List products (Note [(1)], p 23) on which ADR reports have been sent to the International Bank over the two 20-year periods, to sections VO8A A, B, C and D, and finally to contrast-enhanced MR, sections V08C A and B.

In the first paper of the series ([5]) we recalled that "After the 5th meeting of the National Representatives (Portonovo di Ancona, Italy, 1982), the number of reports regarding the Countries for which data were available was weighted using indices of product use". Nevertheless, since this essential procedure was not completed, we still ignore the total number of treatments administered for each combination of use of the contrast agents and the adverse drug effects and/or events (ADRs) reported to and collected by the international World Bank, still the sole body of this kind. This is a negative situation, especially for our studies. We are aware of the insufficiency of the data we are analyzing to draw valid conclusions, but will use them to illustrate a method that we hope will prove useful.

1. Presentation of main reference data on WHO System-Organ class disorders (SOCDs)

Table of Figure 1

Seven products and their numbers of reports, total or for each n. 30 ordered WHO system-organ class disorders (SOCD) codes. Reports sent on 5.7.2010 by Dr. Marie Lindquist, Director, WHO Uppsala Collaborating Center as per 1990-2010 years new PR22-2010 file.

Year 1990-2010

		Amidotrizoate		Iodamide		Iotalamate		Iodoxamate		Ioxaglate		Iohexol		Iopamidol	
	CODICE	18.631	%	277	%	7.144	%	75	%	3.399	%	17.476	%	15.537	%
1	100	6.833	36,68%	91	32,85%	3.784	45,07%	16	21,33%	927	27,27%	4.977	28,19%	3.507	22,04%
2	200	78	0,15%	1	0,36%	34	0,48%		0,00%	14	0,41%	84	0,48%	105	0,67%
3	300	1	0,01%									1	0,01%		
4	410	1.041	5,59%	23	8,30%	343	4,82%	6	8,00%	191	5,59%	2.127	12,05%	2.161	13,82%
5	420											1	0,01%		
6	431	250	1,34%	3	1,08%	112	1,57%			35	1,03%	228	1,30%	247	1,58%
7	432	14	0,08%			7	0,10%			1	0,03%	36	0,21%	34	0,22%
8	433	9	0,05%	1	0,36%	1	0,01%				0,00%	37	0,21%	14	0,09%
9	500	171	0,92%	2	0,72%	54	0,76%	3	4,00%	62	1,77%	334	1,91%	469	3,02%
10	600	2.385	12,80%	39	14,08%	563	7,92%	13	17,33%	427	12,56%	1.618	9,26%	1.503	9,64%
11	700	13	0,07%			2	0,03%			7	0,21%	38	0,22%	20	0,13%
12	800	42	0,23%			10	0,14%			11	0,32%	89	0,51%	79	0,51%
13	900	12	0,06%							6	0,18%	28	0,16%	9	0,06%
14	1010	824	4,42%	17	6,14%	217	3,04%	6	8,00%	272	8,00%	816	4,67%	904	5,78%
15	1020	43	0,23%			7	0,10%			16	0,47%	76	0,43%	78	0,50%
16	1030	633	3,40%	5	1,81%	118	1,65%	4	5,33%	159	4,68%	597	3,42%	565	3,62%
17	1040	627	3,36%	2	0,72%	176	2,46%	5	6,67%	80	2,35%	459	2,63%	455	2,91%
18	1100	2.654	14,25%	40	14,44%	1.248	17,47%	9	12,00%	426	12,53%	2.253	12,89%	2.329	14,89%
19	1210	8	0,04%			2	0,03%			7	0,21%	7	0,04%	11	0,07%
20	1220	16	0,09%			5	0,07%			4	0,12%	36	0,21%	31	0,20%
21	1230	51	0,27%			20	0,28%			21	0,62%	67	0,38%	65	0,42%
22	1300	750	4,03%	3	1,08%	218	3,05%			184	5,41%	721	4,13%	507	3,24%
23	1410		0,00%								0,00%				
24	1420	8	0,04%							2	0,06%	4	0,02%	2	0,01%
25	1500		0,00%									1	0,01%	1	0,01%
26	1600		0,00%									1	0,01%	2	0,01%
27	1700	3	0,02%					1	1,33%			6	0,03%	2	0,01%
28	1810	1.971	10,58%	47	16,97%	691	9,67%	12	16,00%	535	15,86%	2.552	14,77%	2.294	14,97%
29	1820	264	1,42%	3	1,08%	95	1,33%			4	0,12%	249	1,42%	181	1,16%
30	1830	20	0,11%			4	0,06%			4	0,12%	53	0,30%	31	0,20%

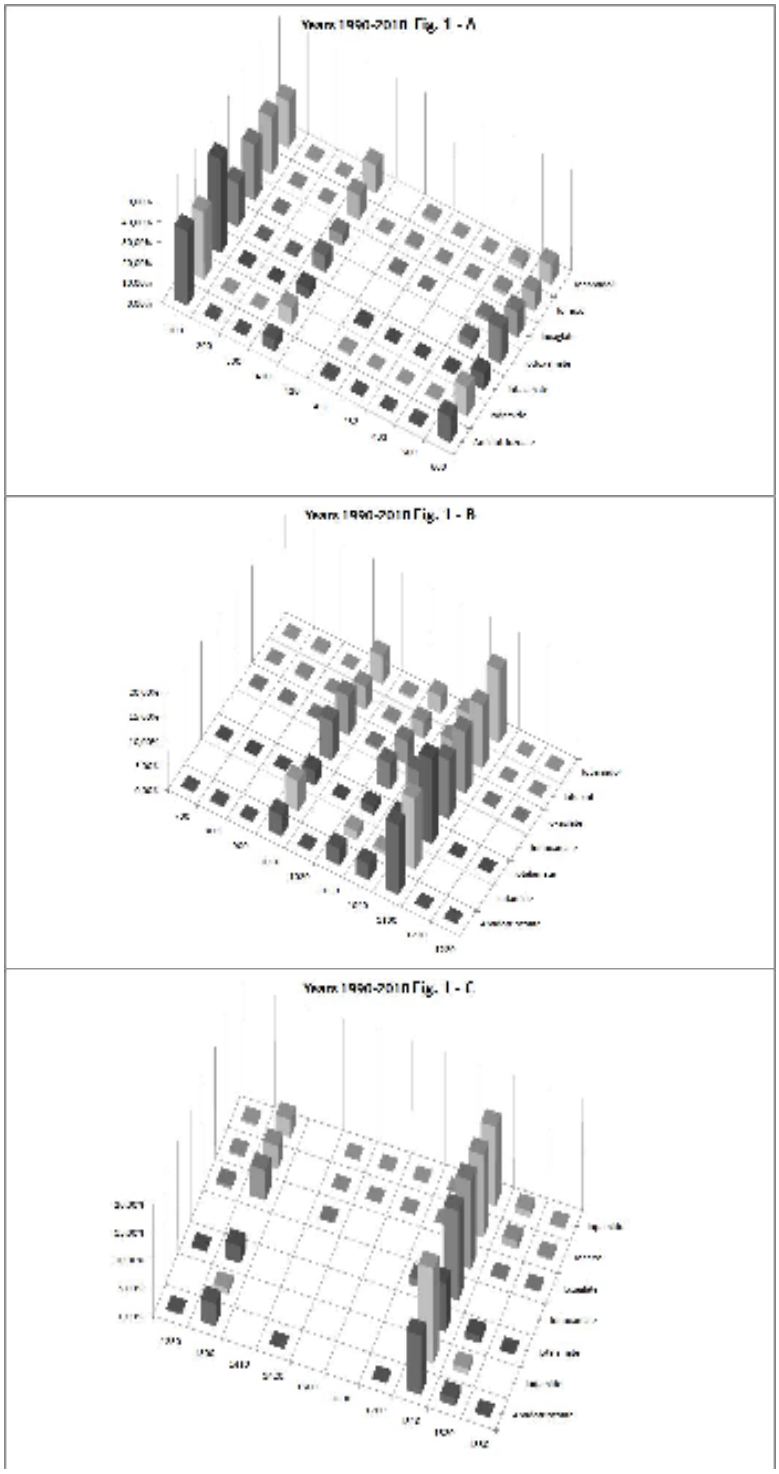


Figure 1

Profiles (A, B, C) each of 10 system-organ class disorders as indicated by their WHO-codes of same 7 contrast agents of previous 1968-1989 twenty years 1st note [5]; y axis, percent number of their aggregated 14 salts as for n 63.471 Reports of the 1990-2010 twenty years new PR22-2010 Files sent 5.7.2010 by Dr Marie Lindquist, Director, WHO-Uppsala Collaborating Centre. Products signaled: 1

- Amidotrizoate - ATC VO8AA, 18.759 (acid, 13.527; meglumine amidotrizoate/sodium amidotrizoate, 5.191; meglumine amidotrizoate/sodium amidotrizoate/calcium amidotrizoate, 16; sodium amidotrizoate/lysine amidotrizoate, 20; sodium aminotrizoate/meglumine, 5); 2 - Iodamide - ATC VO8AA, 278 (iodamide, 260; iodine/iodamide meglumine, 14; meglumine/iodamide sodium, 4); 3 - Iotalamate - ATC VO8AA, 7.189 (acid, 7.153; iotalamate meglumine/iotalamate sodium, 36); 4 - Iodoxamate – ATC VO8AC, 75 (acid, 75); 5 – Ioxaglate – ATC VO8AB, 3.413 (ioxaglate meglumine/ioxaglate sodium, 3.413); 6 – Iohexol – ATC VO8AB, 17.773; 7 - Iopamidol – ATC VO8AB, 15.979. Abscissas, 30 WHO system-organ class disorders (SOCD) and code: 1- 0100, Skin and appendages; 2 - 0200, Musculo-skeletal; 3 – 0300, Collagen; 4 – 0410, Central & peripheral nervous system; 5 – 0420, Autonomic nervous system; 6 – 0431, Vision; 7 – 0432, Hearing and vestibular; 8 – 0433, Special senses; 9 – 0500, Psychiatric; 10 – 0600, Gastrointestinal; 11 – 0700, Liver and biliary; 12 – 0800, Metabolic and nutritional; 13 – 0900, Endocrine; 14 – 1010, Cardiovascular, general; 15 – 1020, Myo-, endo- pericardial & valve; 16 – 1030, Heart rate and rhytm; 17 – 1040, Vascular (extracardiac); 18 – 1100, Respiratory; 19 – 1210, Red blood cell; 20 – 1220, White cell and RES; 21 – 1230, Platelet, bleeding & clotting; 22 – 1300, Urinary; 23 – 1410, Reproductive, male; 24 – 1420, Reproductive, female; 25 – 1500, Foetal; 26 – 1600, Neonatal and infancy; 27 – 1700, Neoplasms; 28 - 1810, Body as a whole, general; 29 – 1820, Application site; 30 – 1830, Resistance mechanism. New SOCD 31 – 2100, Poison specific terms, and 32 – 2000, Secondary term had not been used.

2. A pilot statistical study

2.1. Description of the data

The aim of the exercise is drug auto-classification by means of the adverse reactions. In this pilot study, 7 closely related drugs, all of them contrast media, were followed for a number of years and the numbers of occurrences of 30 adverse reactions were recorded. The result of such a follow-up is a contingency 30x7 data matrix, where the rows correspond to the 30 ADR-SOCDs, and the columns to the 7 drugs: 1=Amidotriozoate; 2=Iodamide; 3=Iotalamate; 4= Iodoxamate; 5=Ioxaglate; 6=Iohexol; 7= Iopamidol. A clustering operation on the columns should display the reciprocal position of the drugs, and in particular show which of them can be lumped together in clusters.

One data set of this type was obtained some twenty years ago from the WHO-Uppsala Bank and analyzed, but the project was interrupted and let to lay dormant until recently. This time, two such data sets, covering each a period of 20 years were graciously offered to us by the WHO-Uppsala Bank; they are displayed in the Table 1A and Table 1B.
The first table sums up 40396 cases and the second one, 62639 cases.

One sees at once that quite a few ADR-SOCDs are very rare, some of them even totally absent. This suggests eliminating the ADR-SOCDs which contribute little to the total number of cases.
We have chosen to eliminate from each data set the scarcest ADR-SOCDs contributing together no more than 1% of the total.
For the 1968-1989 data, this reduced the initial 30x7 matrix to a 14x7 one, with a loss of 0.93 % only (40020 cases instead of 40396). This reduced data set, where the 14 ADR-SOCDs 1 4 6 9 10 14 15 16 17 18 21 22 28 29 were retained, is displayed in Table 2A.

For the 1990-2010 data, this reduced the initial matrix to a 16x7 one, with a loss of only 0.92 % (62065 cases instead of 62639). The reduced data set, where the retained 16 ADR-SOCDs are 1 2 4 6 9 10 12 14 15 16 17 18 21 22 28 29, is displayed in Table 2B.

Table 1A

ADR-SOCDs frequencies for years 1968-1989 from 1st note [5] (matrix X1). Rows 1-30 stand for ADR-SOCDs indicated by their WHO-Uppsala Bank Code. Columns 3-9, caption marked in bold, stand for Drugs as specified: **1=Amidotriozoate; 2=Iodamide; 3=Iotalamate; 4= Iodoxamate; 5=Ioxaglate; 6=Iohexol; 7= Iopamidol.**

Nr Crt	CODE	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	100	9082	175	2479	92	462	292	204
2	200	48	0	21	0	3	21	18
3	300	1	0	0	0	0	0	0
4	410	1529	36	490	16	87	572	576
5	420	0	0	0	0	0	0	0
6	431	352	6	115	4	19	67	51
7	432	23	0	4	2	3	16	16
8	433	14	1	3	0	1	9	7
9	500	313	7	116	8	29	106	73
10	600	2659	103	633	111	258	249	213
11	700	15	0	9	0	3	7	1
12	800	19	0	4	0	3	4	4
13	900	5	0	1	0	0	2	0
14	1010	1668	62	348	32	112	109	123
15	1020	85	2	16	2	15	25	26
16	1030	1025	27	210	18	53	74	93
17	1040	824	9	255	10	41	79	45
18	1100	3714	127	1163	74	177	197	205
19	1210	7	0	0	0	0	0	4
20	1220	15	0	6	0	3	7	1
21	1230	59	0	25	0	10	22	30
22	1300	900	8	242	11	42	58	43
23	1410	2	0	0	0	0	0	0
24	1420	3	0	1	0	0	0	0
25	1500	4	0	0	0	0	0	0
26	1600	0	0	0	0	0	0	0
27	1700	4	0	0	0	0	0	0
28	1810	3402	95	957	70	242	453	315
29	1820	232	1	144	2	3	21	4
30	1830	13	0	9	0	2	6	1

Table 1B (As for Table of Figure 1, Section 1.)

ADR-SOCDs frequencies for years 1990-2010 (matrix X2). Rows 1-30 stand for ADR-SOCDs indicated by their WHO-Uppsala Bank Code. Columns 3-9, caption marked in bold, stand for Drugs as specified: **1=Amidotriozoate; 2=Iodamide; 3=Iotalamate; 4= Iodoxamate; 5=Ioxaglate; 6=Iohexol; 7= Iopamidol.**

Nr Crt	CODE	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	100	6833	91	3284	16	927	4927	3602
2	200	28	1	34	0	14	84	105
3	300	1	0	0	0	0	1	0
4	410	1041	23	343	6	191	2107	2161
5	420	0	0	0	0	0	1	0
6	431	250	3	112	0	35	228	247
7	432	14	0	7	0	1	36	34
8	433	9	1	1	0	0	37	14
9	500	171	2	54	3	60	334	469
10	600	2385	39	566	13	427	1618	1508
11	700	13	0	2	0	7	38	20
12	800	42	0	10	0	11	89	79
13	900	12	0	0	0	6	28	9
14	1010	804	17	217	6	272	816	904
15	1020	43	0	7	0	16	76	78
16	1030	633	5	118	4	159	597	566
17	1040	607	2	176	5	80	469	455
18	1100	2654	40	1248	9	428	2253	2329
19	1210	8	0	2	0	7	7	11
20	1220	16	0	5	0	4	36	31
21	1230	51	0	20	0	21	67	65
22	1300	750	3	218	0	184	721	507
23	1410	0	0	0	0	0	0	0
24	1420	8	0	0	0	2	4	2
25	1500	0	0	0	0	0	1	1
26	1600	0	0	0	0	0	1	2
27	1700	3	0	0	1	0	6	2
28	1810	1971	47	621	12	539	2582	2224
29	1820	264	3	95	0	4	249	181
30	1830	20	0	4	0	4	63	31

Table 2A

ADR-SOCDs frequencies for years 1968-1989 reduced by about 1%, by deleting 16 rows with smallest ADR values (and obtaining matrix X1R). This amounts to neglecting only 0.93% of the total number of ADR-SOCDs. The Nr Crt and the CODE are those of Table 1A for X1.

Nr Crt	CODE	1	2	3	4	5	6	7
1	**100**	9082	175	2479	92	462	292	204
4	**410**	1529	36	490	16	87	572	576
6	**431**	352	6	115	4	19	67	51
9	**500**	313	7	116	8	29	106	73
10	**600**	2659	103	633	111	258	249	213
14	**1010**	1668	62	348	32	112	109	123
15	**1020**	85	2	16	2	15	25	26
16	**1030**	1025	27	210	18	53	74	93
17	**1040**	824	9	255	10	41	79	45
18	**1100**	3714	127	1163	74	177	197	205
21	**1230**	59	0	25	0	10	22	30
22	**1300**	900	8	242	11	42	58	43
28	**1810**	3402	95	957	70	242	453	315
29	**1820**	232	1	144	2	3	21	4

Table 2B

ADR-SOCDs frequencies for years 1990-2010 reduced by about 1%, by deleting 14 rows with smallest ADR values (which leaves matrix X2R). This amounts to neglecting only 0.92 % of the total number of ADR-SOCDs. The Crt Nr and the CODE are those of Table 1B for X2.

Crt Nr	CODE	1	2	3	4	5	6	7
1	**100**	6833	91	3284	16	927	4927	3602
2	**200**	28	1	34	0	14	84	105
4	**410**	1041	23	343	6	191	2107	2161
6	**431**	250	3	112	0	35	228	247
9	**500**	171	2	54	3	60	334	469
10	**600**	2385	39	566	13	427	1618	1508
12	**800**	42	0	10	0	11	89	79
14	**1010**	804	17	217	6	272	816	904
15	**1020**	43	0	7	0	16	76	78
16	**1030**	633	5	118	4	159	597	566
17	**1040**	607	2	176	5	80	469	455
18	**1100**	2654	40	1248	9	428	2253	2329
21	**1230**	51	0	20	0	21	67	65
22	**1300**	750	3	218	0	184	721	507
28	**1810**	1971	47	621	12	539	2582	2224
29	**1820**	264	3	95	0	4	249	181

The Table 3A and Table 3B display the drug profiles (in %) for the reduced data.

Table 3A

Percent per Drug Distribution of cases among ADR-SOCDs for the reduced data, years 1968-1989. The values of this table are obtained from those of Table 2A, as percents of the Drug totals. If one divides all the values by 100, one obtains the Drug Profiles.

		DRUGS						
Nr	**CODE**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	**100**	35.14	26.60	34.46	20.44	29.81	12.56	10.19
4	**410**	5.92	5.47	6.81	3.56	5.61	24.61	28.79
6	**431**	1.36	0.91	1.60	0.89	1.23	2.88	2.55
9	**500**	1.21	1.06	1.61	1.78	1.87	4.56	3.65
10	**600**	10.29	15.65	8.80	24.67	16.65	10.71	10.64
14	**1010**	6.45	9.42	4.84	7.11	7.23	4.69	6.15
15	**1020**	0.33	0.30	0.22	0.44	0.97	1.08	1.30
16	**1030**	3.97	4.10	2.92	4.00	3.42	3.18	4.65
17	**1040**	3.19	1.37	3.55	2.22	2.65	3.40	2.25
18	**1100**	14.37	19.30	16.17	16.44	11.42	8.48	10.24
21	**1230**	0.23	0.00	0.35	0.00	0.65	0.95	1.50
22	**1300**	3.48	1.22	3.36	2.44	2.71	2.50	2.15
28	**1810**	13.16	14.44	13.30	15.56	15.61	19.49	15.74
29	**1820**	0.90	0.15	2.00	0.44	0.19	0.90	0.20

Table 3B

Percent per Drug Distribution of cases among ADR-SOCDs for the reduced data, years 1990-2010. The values of this table are obtained from those of Table 2B, as percents of the Drug totals. If one divides all the values by 100, one obtains the Drug Profiles.

		DRUGS						
Nr Crt	**CODE**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	**100**	36.88	32.97	46.10	21.62	27.52	28.62	23.27
2	**200**	0.15	0.36	0.48	0.00	0.42	0.49	0.68
4	**410**	5.62	8.33	4.82	8.11	5.67	12.24	13.96
6	**431**	1.35	1.09	1.57	0.00	1.04	1.32	1.60
9	**500**	0.92	0.72	0.76	4.05	1.78	1.94	3.03
10	**600**	12.87	14.13	7.95	17.57	12.68	9.40	9.74
12	**800**	0.23	0.00	0.14	0.00	0.33	0.52	0.51
14	**1010**	4.34	6.16	3.05	8.11	8.08	4.74	5.84
15	**1020**	0.23	0.00	0.10	0.00	0.48	0.44	0.50
16	**1030**	3.42	1.81	1.66	5.41	4.72	3.47	3.66
17	**1040**	3.28	0.72	2.47	6.76	2.38	2.72	2.94
18	**1100**	14.33	14.49	17.52	12.16	12.71	13.09	15.05
21	**1230**	0.28	0.00	0.28	0.00	0.62	0.39	0.42
22	**1300**	4.05	1.09	3.06	0.00	5.46	4.19	3.28
28	**1810**	10.64	17.03	8.72	16.22	16.00	15.00	14.37
29	**1820**	1.42	1.09	1.33	0.00	0.12	1.45	1.17

Figure 2A and Figure 2B display the drug profile curves for the reduced data, based on Table 3A and Table 3B respectively.

Figure 2A - Drug Percent Curves. The abscissas are Crt Nrs of the ADR-SOCDs in Table 3A, and correspond to 1 4 6 9 10 14 15 16 17 18 21 22 28 29 (e.g. the abscissa 11 corresponds to ADR-SOCD 21).

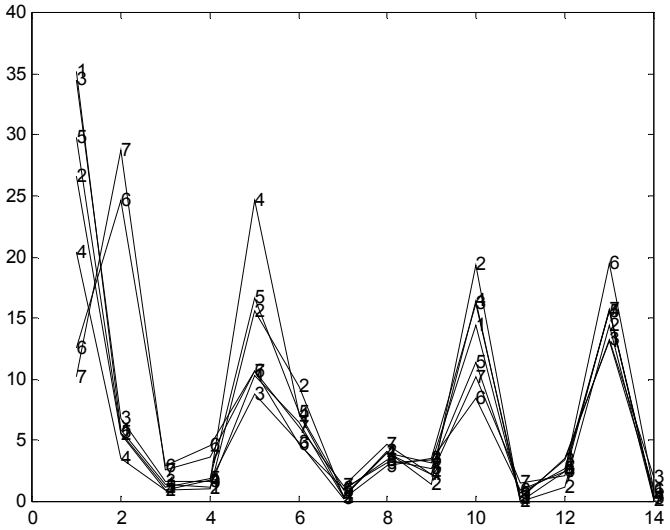
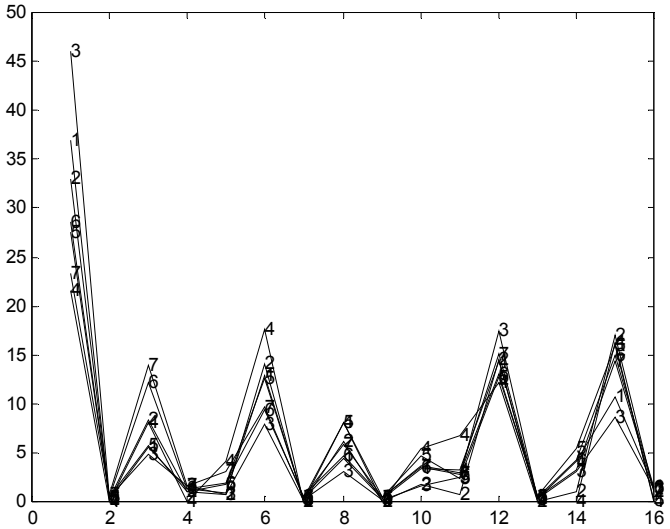


Figure 2B - Drug Percent Curves. The abscissas are Crt Nrs of the ADR-SOCDs in Table 3B, and correspond to 1 2 4 6 9 10 12 14 15 16 17 18 21 22 28 29 (e.g. the abscissa 11 corresponds to ADR-SOCD 17).



These plots show that even with such a small number of drugs, the problem of their objective grouping is not trivial.

2.2. Drug Clustering

Both data sets X1R and X2R are contingency (r x c) tables N={ n_{ij} : i = 1,2,...,r; j= 1,2,...,c}, with nonnegative elements; for both, c= 7, while r takes the values 14 and 16 respectively. Each combination (i, j) is a cell of the table, with which are associated the cell value n_{ij} (known) and the cell probability p_{ij} (unknown). Denote by n_{i+} the sum of row i , by n_{+j} the sum of column j and by n_{++} the total sum of elements of N.
The same is done for the table P= {p_{ij}} of cell probabilities, defining the row probabilities p_{i+} , the column probabilities p_{+j} ,and the total probability p_{++}= 1.
For both data sets, the columns correspond to the 7 drugs. Each column is a vector of length r= 14 or r= 16, respectively.
If one divides all the elements of column j by the column total n_{+j}, one obtains **the column j profile**, a vector of weights summing up to 1. Two columns have **the same profile** if and only if they have **proportional elements**, i.e. the elements of one column can be obtained from those of the other column by multiplying by the same nonzero factor. The same can be done for the table P, obtaining the **probability column profiles.**
Independence means that the table P of probabilities is such that **all column profiles coincide** or, in other words, that the hypothesis H_0: p_{ij}= p_{i+} p_{+j} for all cells (i, j) is satisfied.
The **Likelihood-Ratio Test Statistic for testing H_0 against the general alternative is the WILKS's CHI SQUARE:**

W= the sum of n_{ij} log (n_{ij} n_{++}/n_{i+} n_{+j}), for all cells (i,j) of the table.

The statistic W takes the value zero for a table N where all the columns have the same profile or, in other words N has the multiplicative structure n_{ij} = n_{i+} n_{+j}/n_{++} for all cells
(i, j). For tables which depart from this structure, W takes values increasing with the severity of this departure. This leads to the idea of **using W as a global measure of dissimilarity between columns.**

We define the **Diameter of a subtable** formed of columns, as the value of W for this subtable.
At one end, we have the diameter of the set N itself; on the other end, the diameters of the subtables formed of just two columns. In the latter case, we will use for diameter the term of **squared WILKS inter-column pseudo-distance** (noting that this is a dissimilarity measure and not a proper distance). The inter-column pseudo-distance will be square root of this dissimilarity measure. A very useful property of W is that of **monotonicity:** if N1 and N2 are such that N1 is a subtable of N2, and W1 and W2 are their respective WILKS statistic values, then W1 does not exceed W2.

The distribution of the WILKS statistic, in the case of independence, is very well approximated by that of a **Chi Square** with a number of degrees of freedom df =
(nr of rows-1)(nr of cols-1).

We will say also that a set of columns is **homogeneous**, if the subtable they form displays independence, that is if the involved columns may be considered as generated by sampling from the same multinomial distribution.
Our aim is to group the columns (drugs in our case) **into clusters.** A cluster is a **maximal homogeneous set of columns.** It has to be maximal, that is such that any larger subset including it will be non-homogeneous. **The diameter** of the above subtable **can be used to check the homogeneousness.** Assume that we have k columns, hence a (k x n_c) subtable. Under independence, the diameter is distributed as a Chi square with df= (k-1)(n_c-1) degrees of freedom. The check itself

will consists from comparing the diameter to a gauge equal to the critical .95 point, say, of the Chi square with df= (k-1)(n_c-1), and rejecting homogeneousness if the diameter exceeds this gauge. This test will have a significance level of .05.

This is true if the above k rows were selected at random, or on theoretical grounds, and not as a result of the examination of the data. **In our case, the subsets will be obtained precisely by a data-driven algorithm.** To achieve an overall significance level of (at most) .05, we have to **operate within a Simultaneous Testing Procedure (STP)**, where the above gauge is replaced by **the STP gauge**. In the **STP of KR GABRIEL** [7]**,** instead of the above df one takes the value df= (n_r -1) (n_c -1) , i.e. **the degrees of freedom of the Chi square for the whole table.**

Our technique, based on the WILKS's statistic, and GABRIEL's STP, will consist from:

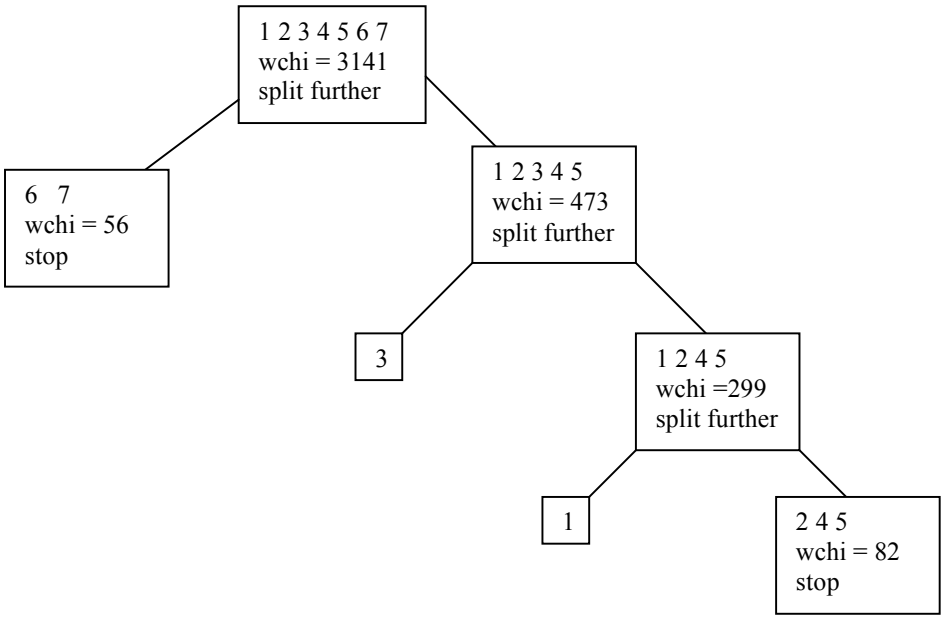
a) **A binary tree clustering based on a clustering technique for optimally splitting a set into two subsets.** This technique is based on the WILKS's inter-column squared pseudo-distance. Each subset is tested within GABRIEL's STP described above. If the diameter of the subset does not exceed the STP Gauge, hence the subset is found to be homogeneous, this branch of the tree terminates here and the subset is declared a cluster. Else, the procedure continues: the subset is split into two subsets and the STP test is applied to each of them.
The resulting binary tree will show the clusters as the ends of the branches.

b) **A graphical procedure whose result is an Euclidean Map** where the columns of the table are represented by markers, **the Euclidean distances between markers approximating the WILKS's inter-column pseudo-distances.** One starts from the matrix of WILKS Chi Squared column pair-wise dissimilarities, and by means of the Torgerson-Gower Multi-Dimensional Scaling, one obtains a "reification", that is a set of points in an Euclidean space, whose pair-wise Euclidean distances approximate the pair-wise dissimilarity pseudo-distances. The coordinates are ordered in decreasing importance, and the first two are used in the Euclidean Map which permits to see the cluster structure of the columns to an extent which **will confirm the clustering already obtained.** This Euclidean Map is in general close to the Correspondence Analysis first two components plot.

This is true provided the GOF (Goodness of Fit) given by the fist two dimensions is high.
Otherwise, some of the pair-wise dissimilarities may be poorly approximated.

In Figure 3A and Figure 3B are shown the binary clustering trees for the reduced
data sets for years 1968-1989 and 1990-2010, respectively.
The **Diameter of a subtable of columns**, that is the WILKS's statistic value for the subtable, **is denoted in the figure by "wchi"**. The degrees of freedom for the two data sets are (14-1)*(7-1) = **78** and (16-1)*(7-1) = **90**, respectively. That gives for the respective STP Gauges the values chi2inv (.95, 78) = **99.62** and chi2inv (.95, 90) = **114.81**. A subset of drugs will be declared a cluster if its **wchi** value does not exceed the respective **STP Gauge**, or else will have to be split further. The values of the statistic wchi are rounded to integers.

Figure 3A - Binary Clustering Tree for the Reduced Data Set 1968-1989

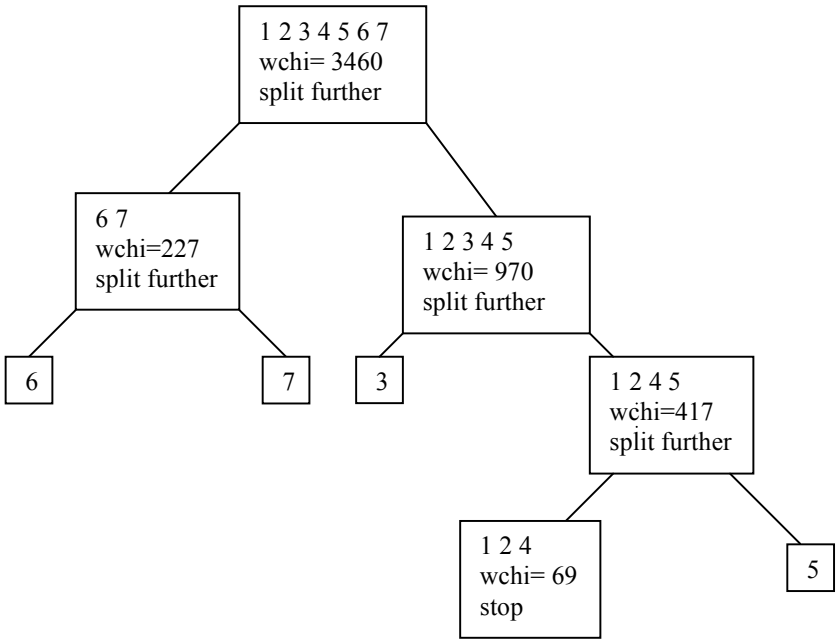


Here **the clusters are**: **[1], [2 4 5], [3], [6 7].**

But there is much more information in this tree. The value of the diameter wchi at a node of the tree is an upper bound for the squared WILKS pair-wise pseudo-distances of the involved columns because of the monotonicity property of wchi. Even if this is not an exact bound, some heuristic conclusions may be drawn.

For example, for the total set S = [1, 2, 3, 4, 5, 6, 7] one has the diameter w = 3141. For its subset S1 = [6, 7], the diameter is w1 = 56 and for its subset S2 = [1, 2, 3, 4, 5], the diameter is w2 = 473. The pair-wise squared WILKS pseudo-distances between pairs of columns both in either S1 or S2 are bounded by 56 and 473 respectively. The much larger upper bound 3141 motivates us to infer, even if non-rigorously, that the maximum of the squared pseudo-distance should will be attained for a pair of columns, one of which is in S1 and the other in S2. And indeed, this maximum of 1480 is reached for the pair of columns 7 and 1.
This exemplification can be continued, but we will not do this, neither here or for the remaining data sets.

Figure 3B - Binary Clustering Tree for the Reduced Data Set 1990-2010



The **clusters are here: [1 2 4], [3], [5], [6], [7]**.

Figure 4A displays a confirmatory Euclidean plot for the clustering results of Figure 3A.The GOF=.9938 for the first two axes is very good, and so is the plot where the clustering results are faithfully reproduced.

Figure 4B displays a confirmatory Euclidean plot for the clustering results of Figure 3B.The GOF=.9545 for the first two axes is mediocre. The plot can still serve, but only partially for confirmation. The markers for drugs 1, 3 appear close (which is wrong) and the marker of drug 1 appears far of the markers 2, 4 (which is again wrong). The correct spatial configuration was distorted by projection on the first two axes.

Figure 4A

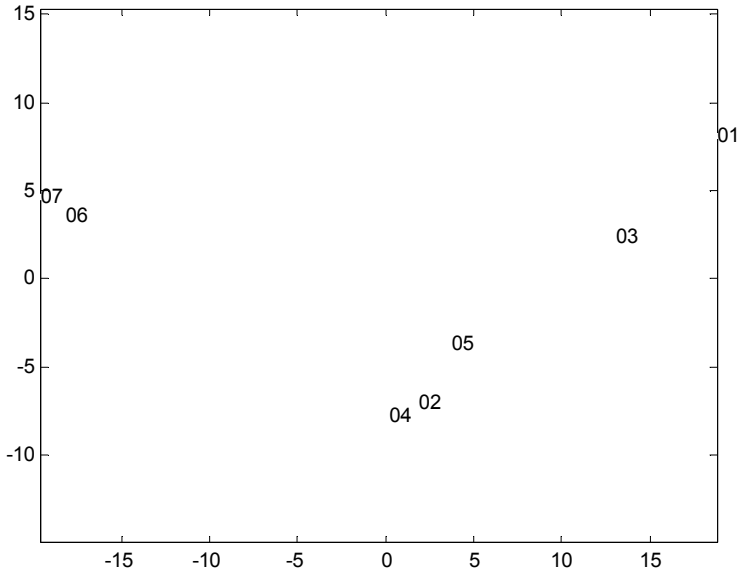
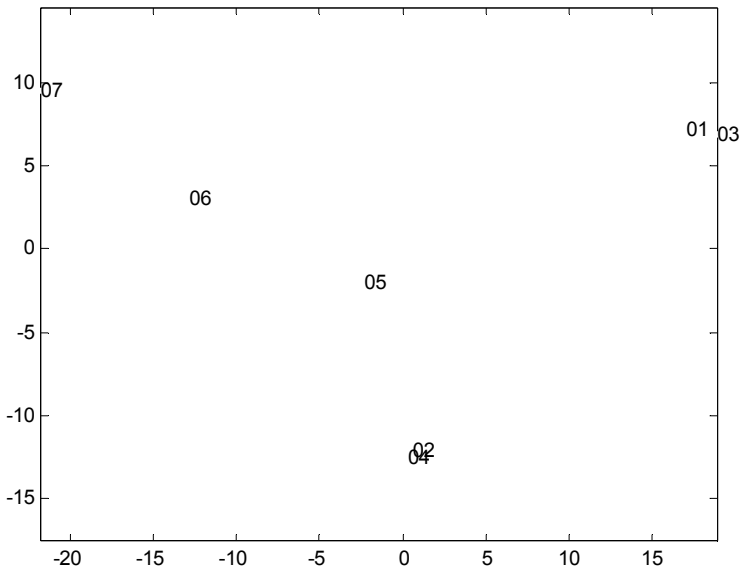


Figure 4B



2.3. Comparison of clustering results for 1968-1989 and 1990-2010

Examining the results and especially the cluster trees for the two data sets, one sees a partial but significant similitude.
The ADR-SOCDs retained in the data reduction operation are almost the same; only ADR-SOCDs 2 and 12 were added to the 14 retained in the first reduced data set in order to obtain the second one.

In both binary cluster trees, one has the same segments

from [1 2 3 4 5 6 7] to [6 7],
from [1 2 3 4 5 6 7] to [1 2 3 4 5],
from [1 2 3 4 5] to [3],
from [1 2 3 4 5] to [1 2 4 5].

In addition, in both binary cluster trees, the drugs 2 and 4 enter together in a same cluster.

The apparent differences are that in the second data set drugs 6 and 7 don't form anymore a cluster, but are separated in two singletons, and that drugs 1 and 5 change roles in passing from one cluster tree to the second. In the first case at least, the difference can be
ascribed to the fact that in the second data set there are by about 50% more records than in the first one and this leads to an increased precision.

3. Presentation of original data on WHO ordered preferred terms of adverse drug reactions and events (ADRs)

3.1. Tables and Legends

Table 4A

Number of the adverse reactions (ADRs) and/or events according to their preferred name and code, as from the reports collected in the WHO-Uppsala International bank, records sent 5.7.2010 by Dr. Marie Lindquist, Director, WHO-Uppsala Collaborating Center as per 1968-1989 PR22-2010 file. The percent of the total number for each indicated of the same seven products (columns) and of the most frequent, and/or highest percentuals (rows), are included for each of the six system-organ-class disorder (SOCD) codes presenting for the two twenty years periods at least 97% of their total aggregated values in the 30 classes of the previously presented Tables and Figures of the 1st [5], and present paper. The total ADRs/events numbers to obtain the % values for each product and class are those of the Table 1 of the reference [5]. Order and name of the six screened SOCDs: 1 (0100) Skin and appendages; 2 (0410) Central & peripheral nervous system; 3 (0600) Gastrointestinal; 4 (1010) Cardiovascular general; 5 (1100) Respiratory; 6 (1810) Body as a whole, general. There are no ADRs/events where in the Table there are 0 values throughout; for the two periods the highest numbers of ADRs/events were for Amidotrizoate, accepted then as common reference.

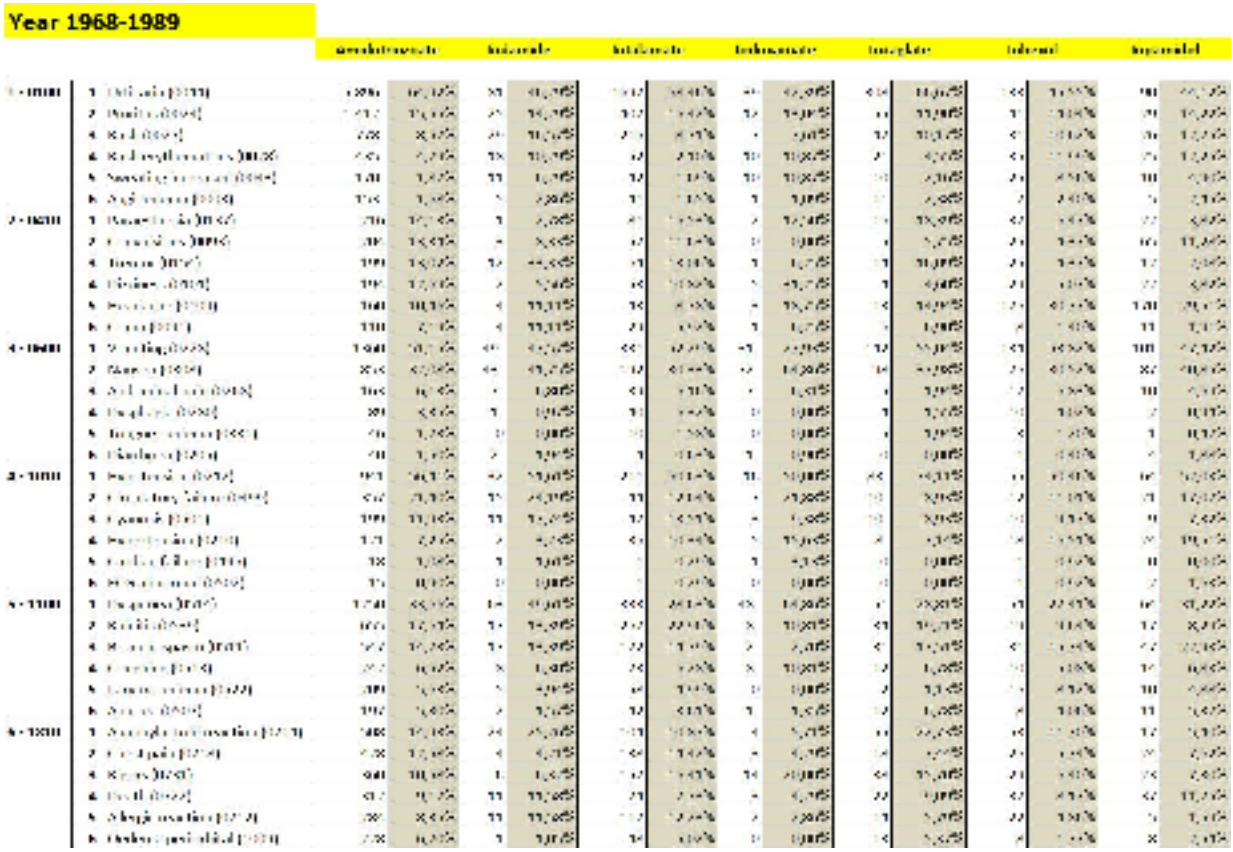
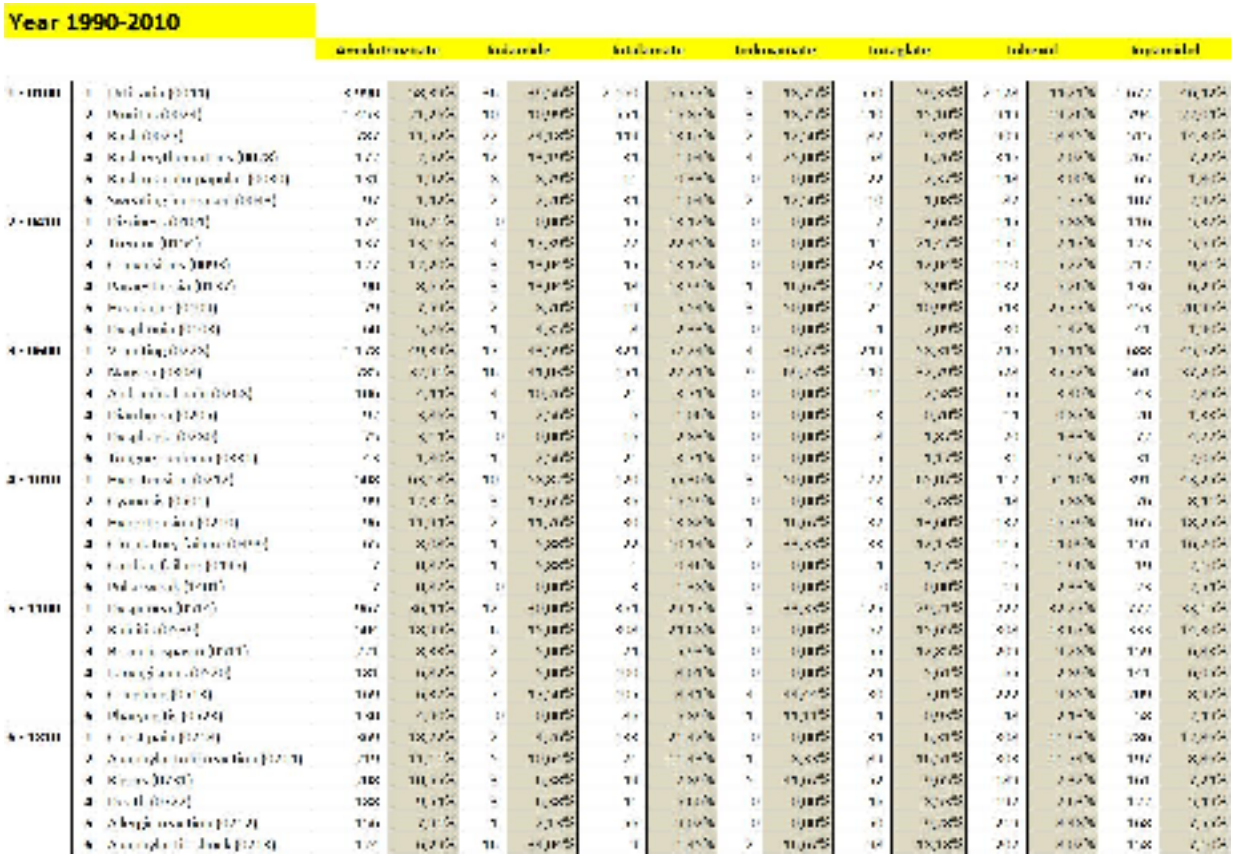


Table 4B

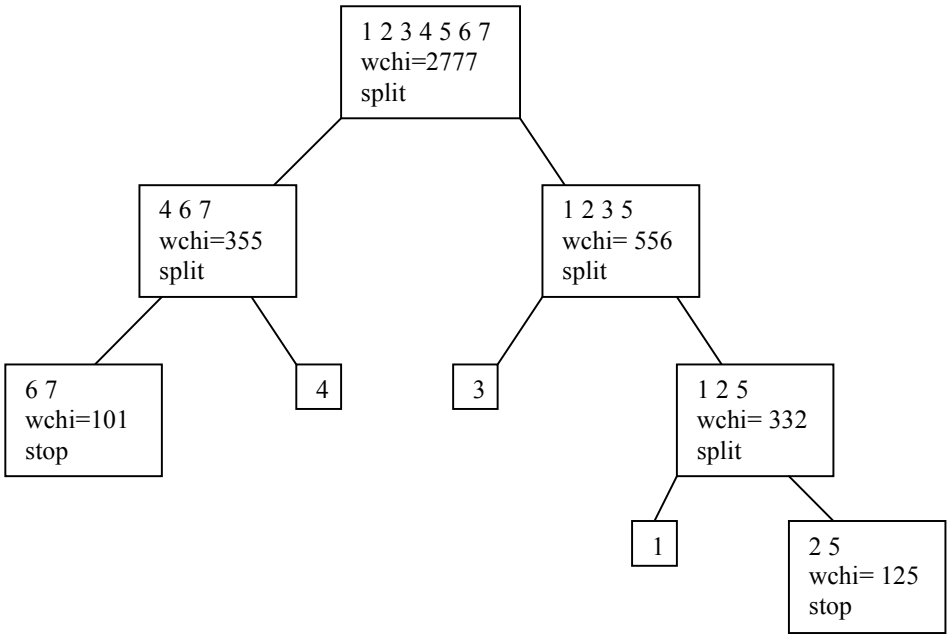
Number of the adverse reactions (ADRs) and/or events according to their preferred name and code, as from the reports collected in the WHO-Uppsala International bank, records sent 5.7.2010 by Dr. Marie Lindquist, Director, WHO-Uppsala Collaborating Center as per 1990-2010 PR22-2010 file. The percent of the total number for each of the same seven indicated products (columns) and of the most frequent, and/or highest percentuals (rows), are included for each of the six system-organ-class disorder codes presenting for the two twenty years periods at least 97% of their total aggregated values in the 30 classes of the previously presented Tables and Figures of the 1st [5], and present paper. The total ADRs/events numbers to obtain the % values for each product and class are those of Table 1 of the present paper. Order and name of the six screened SOCDs: 1 (0100) Skin and appendages; 2 (0410) Central & peripheral nervous system; 3 (0600) Gastrointestinal; 4 (1010) Cardiovascular general; 5 (1100) Respiratory; 6 (1810) Body as a whole, general. No ADRs/events where in the Table there are 0 values; for the two periods the highest numbers of ADRs/events were for Amidotrizoate, then accepted as reference.



3.2. Statistical results for these data sets

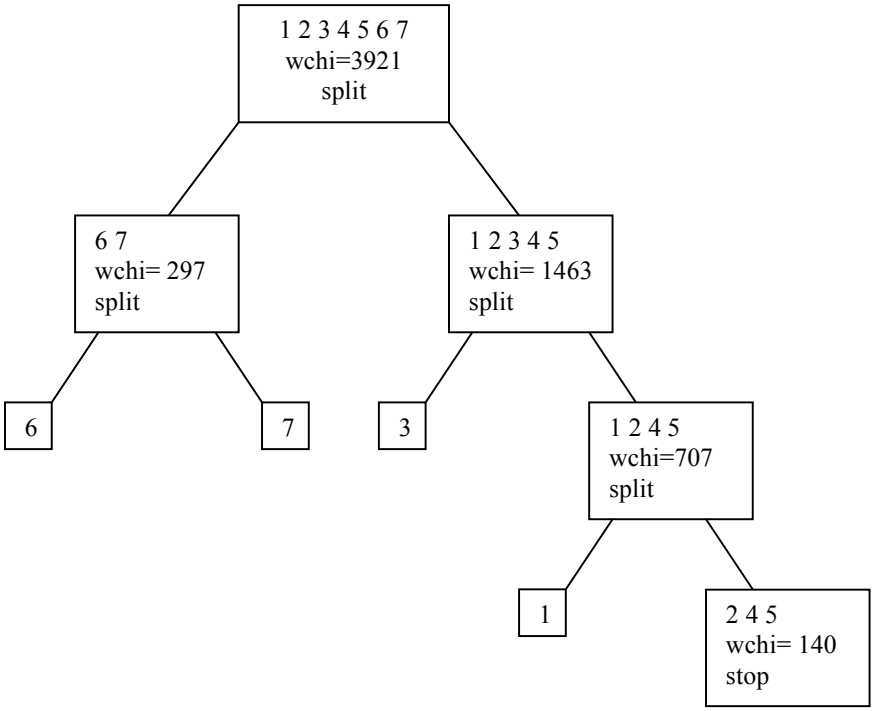
In Figure 5A and Figure 5B are shown the binary clustering trees for the Data Sets of 36 ADRs grouped in six SOCDs, for years 1968-1989 and 1990-2010, respectively.
The degrees of freedom for the two data sets are both equal to (36-1)*(7-1) = **210**. That gives an STP Gauge equal to chi2inv (.95, 210) = **244.81** for both data sets.. A subset of drugs will be declared a cluster if its **wchi** value does not exceed the respective **STP Gauge**, or else will have to be split further. The values of the statistic wchi are rounded to integers.

Figure 5A - Data Set of 36 ADRs grouped in six SOCDs, years 1968-1989



The **clusters are here: [1], [2 5], [3], [4], [6 7]**

Figure 5B – Data Set of 36 ADRs grouped in six SOCDs, years 1990-2010



The **clusters are here: [1], [2 4 5], [3], [6], [7].** This binary tree is almost identical with that of Figure 3A, Section 2.2 (years 1968-1989).

Figure 6A displays a confirmatory Euclidean plot for the clustering results of Figure 5A. The GOF=.9766 for the first two axes is acceptable, and so is the plot which can be used, with circumspection, for checking clustering results.

Figure 6B displays a confirmatory Euclidean plot for the clustering results of Figure 5B. The GOF=.9276 for the first two axes is mediocre. The plot can still serve for confirmation, but only partially and if used with circumspection.

Figure 6A

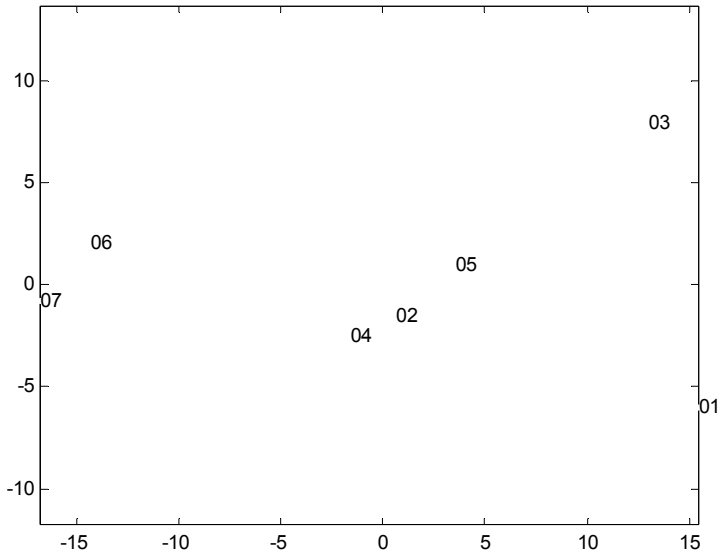
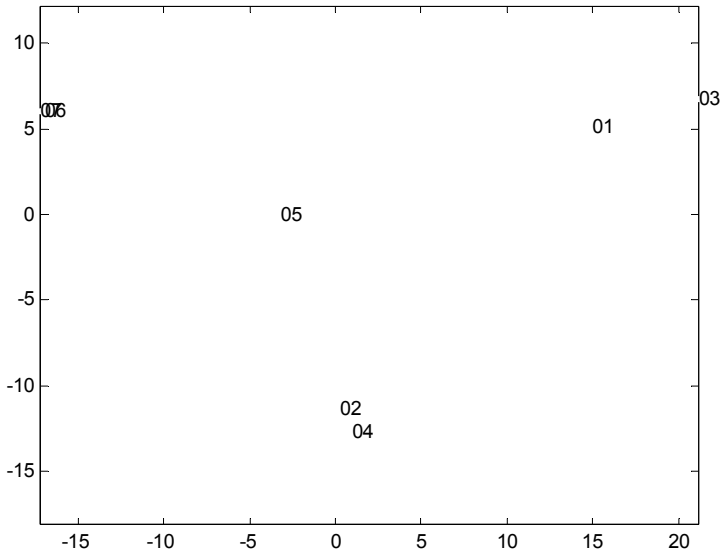


Figure 6B



4. Discussion

In this paper a new objective autoclassification method was applied to the data regarding the first two 20-year periods in which global ADR reports have been collected by the still only international body devoted to this task, the WHO-Uppsala Centre. The two periods span roughly 40 years, from 1968, the time of the Centre's foundation, to 1989, and from 1990 to July 2010. The paper compares first the data regarding the seven most widely used iodinated products applied in contrast-enhanced diagnostic imaging to the number of ADR reports, grouped into the 30 SOCDs approved at the annual meetings of the national representatives of the Countries participating in the WHO Pharmacovigilance Programme.

Still awaiting the data, whose release was approved on the occasion of the 5th Meeting (1982, Portonovo di Ancona, Italy), which will probably be able to be used as information on the number of patients treated and/or the coherence of use/ compliance when they are finally provided (at least by the Countries that have already adhered, adopting an efficient organization), we subjected the available data first to a preliminary normalization. The reports were ordered with reference to the products' WHO preferred names, presenting the data as aggregations into the 30 SOCDs, and then as percent of all the reports received in each 20-year period. These data were then analyzed using a new technique, which was applied to those product classes (and relevant components of individual reactions) that accounted for the largest number of reports, with frequencies > 97% in both 20-year periods. Since the other conditions have not changed, this allowed making at least a quantitative comparison among the various products. These were grouped by their characteristics to enable assessment of the association of their ADRs with their chemotoxicity features in experimental lethal, acute tests and with the indices of their chemical-physical properties e.g. lipophilicity, and, respectively, ionization, osmolality, aggregation and viscosity ratios, organotropism and molecular bond affinity.

In the two periods examined, the largest differences among the 6 classes examined—which were found to share similar overall trends—were between class 1 - 0100, Skin and Appendages Disorders, and class 4 - 0410, Central & Peripheral Nervous System Disorders, in relation to the two VO8AB ratio 3 non-ionic monomers iohexol (6) and iopamidol (7), belonging to the ATC subclass. Differences were respectively of 16.00 and 13.10 %, rising with the global spread of product use and the growing number of reports from 2,396 to 17,476 (for iohexol) and from 2053 to 19,584 (for iopamidol), with a mean increase of 526.98 %. However the literature, by now a very large body compared with the one reported in [5], is not updated here; the reader is referred to the bibliography of some of the more recent reviews (Cf. [8]. No reviews have been published after Morris & Fischer's, in Ann Rev Pharmacol Toxicol 1986;26:143-160 [22], and none is being planned. As an example, in The London Pharmaceutical Press' Martindale Pharmacopoeia online edition, n 182 references are listed available for diatrizoate only at July 2, 2010 revision & update).

The clustering based on WILKS's statistic gave results which were found to be consistent in three of the four data sets on which the technique was applied. Namely in the two datasets of Section 2.1 (years 1968-1989 and 1990-2010), and in the second data set of Section 3 (years 1990-2010). The results for the first data set of Section 3 (years 1968-1989) are not in tune with the rest.
An interesting point comes out from reading the paper "Drug target identification using side-effect similarity" by Campillos M et al., (Science 2008) (Cf [2]), whose authors followed a path slightly overlapping ours and report valuable results. The approach in the above mentioned research was to examine a large set of drugs looking for pairs of drugs applicable to at least one common target. It was

found that similarity of side-effects is increasing significantly the chance of finding such pairs and, surprisingly, that the two members of such a pair can be quite different in composition and have quite different intended therapeutic aims. This in our case alleviates the worry caused by data sets which do not "behave" as expected, and in the same time shows that reading the message sent by the drug ADR-SOCDs profiles proves to be a task more difficult than anticipated.

We intend to examine, with the kind support of WHO-Uppsala Bank, a large set of drug ADR-SOCDs data sets, not only within classes of probably close ones, but en bloc, in order to both check our techniques and find subclasses of interest. We intended at this preliminary stage to keep things clear and simple. We will however explore alternative techniques which may improve the reach and the precision of our results.

Other differences will be able to be analyzed after all the products of the current ATC subclasses that were associated with the largest number of reports have been processed and reclassified ([1], p 23); other papers now being planned will examine the data already available, as reported in the Introduction. These products therefore include the ionic ratios of the new synthetic dimers and also of those introduced over the last two decades, i.e. nonionic dimers that are now iso-osmolar with plasma and have an even higher contrast index, hoping not only to assess comprehensively their risk/benefit ratios and cost-effectiveness, but also to reformulate more precisely the associations of the chemotoxicity factors, for instance in addition to the trends reported in 2000 by Thomsen & Morcos [9] for the 15 products they examined (Cf Fig 2 a, b), which however do not include iodamide (2) and iodoxamate (4). For other data regarding the products mentioned this far, we are positive that the Tables and Figures of the first two papers [5] and of the present contribution are clear and easily interpreted.

The international data collection and grouping system offers some scope for improvement, first of all through the addition of econometric data (standardized as daily dose, DDD and similar, including cost also in terms of currency exchange rates), with predominantly biomedical/sanitary purposes; through improvement of the pathophysiological stratification of the same individuals subjected to diagnostic imaging, on the basis of the history of their (new) requirements; and by highlighting where possible and appropriate the information provided by biological markers of genetic and epigenetic typing. It has become clear that the information given by the ADRs, aggregated into classes of disorders, tends to obscure individual reactions, even the rarer, more severe single events, that have not yet been taken into deep consideration here, and which, it is hoped, will soon be the object of a due change.

To highlight the initiatives taken also by our National Collaboration Service, it will be sufficient to recall here that the Adverse Drug Reaction Bulletin is still being distributed in Italy (also in Italian). In a very recent issue (194, April 2010 [9]), with reference to patients on antihypertensive medications as well as to other patients, the Bulletin stated again the absolute need for using cohorts, better to monitor patients who have experienced an ADR, for identifying them as such and for recalling them (electronically) for checks and therapy adjustments. Here is a confirmation of the usefulness of the global network created by WHO – ITA / ITA – OMS.

From another, final point of view, the line of our contribution is actually addressing to the research evidence gaps, and to the needs of more formal syntheses of currently available knowledge in the field (Cf [11]).

Note[(1)]. ATC International classification of the products of interest, now partially followed by WHO-Uppsala Centre PR22-2010 May 7 file, as presented by Informatore Farmaceutico, 70th Ed 2010, Elsevier Italia, Milan. Our previous selection of the seven most reported products and their code numbers are written in italics: **V08**-Contrast agents; **V08AA**: acetrizoate, *amidotrizoate (diatrizoate) (1)*, diodone (synonymous: iodopyracet), iocarmate, *iodamide (2)*, ioglic(ic)ate, *iotalamate (3)*, ioxitalamate, methiodal, metrizoate; **V08AB**: iobitridol, iodixanol, *iohexol (6)*, iomeprol, *iopamidol (7)*, iopentol, iopromide, iotrolan, ioversol, *ioxaglate (5)*, ioxilan, metrizamide; **VO8AC**: adipiodone (synonymous: iodipamide), iobenzamate, iocetamate, *iodoxamate (4)*, ioglycamate, iopanoate, iopodate, iotroxate, tyropanoate; **V08AD**: iodized fatty acid ethyl esters; iofendylate, iopydol, propyliodone.

Acknowledgement

The series of contributions to which this paper belongs began with the approval by the ad hoc Scientific Committee of the Italian Health Ministry Study Centre, on 1st September 1991, of the Final Report on the Contract with Ancona University, Chair of Pharmacology (headed by Luigi Rossini) signed by the same Ministry on 13th January 1989, entitled "Development of a statistical-modelling programme for assessing the consumption and the benefits and resources of some groups of drugs using the data of the cofounded WHO-Uppsala data bank". Ancona University received on 26th November 1993 from the chairman of the Study Centre the document CS/413/FARM/93/AG 1526, approving the continuation of the research work, to be paid 60 million Lire, a sum which to date has, inexplicably, never been received.
The same co-author (L.R.) unsuccessfully resubmitted the project to AIFA as an independent research until the 2007/2008 plan included. This is felt to be relevant to what is reported in Section 5., especially in the context of ref [60], of the collateral contribution submitted, cited below under [6].

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CAVEAT DOCUMENT

Accompanying statement to data released from the WHO Collaborating Centre

The WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, receives summary clinical reports about individual suspected adverse reactions to pharmaceutical products from National Centres in countries participating in a Collaborative Programme. Only limited details about each suspected adverse reaction are received by the Centre. This imposes certain limitations and qualifications which apply to the information and its use are understood.

The term "pharmaceutical product" is used instead of "drug" to emphasise that product and excipient content, presentation as well as name may vary in their content and format and other procedures, both in time and from place to place.

The reports submitted to the Collaborating Centre in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event.

The reports, which are submitted to National Centres, come from both regulatory and voluntary sources. Some national Centres accept reports only from medical practitioners; other National Centres accept reports from a wide spectrum of health professionals. Some National Centres include reports from pharmaceutical companies in the information submitted to the Collaborating Centre; other National Centres do not.

The volume of reports for a particular pharmaceutical product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time, from product to product and country to country. Moreover, no information is available on the number of patients exposed to the product.

Thus the source of reports accepted by National Centres vary, as do the proportions.

A number of National Centres reach a decision concerning the Collaborating Centre make an assessment of the likelihood that a pharmaceutical product caused the suspected reaction. Other National Centres do not. Comments such assessments on individual reports in the WHO database.

Processing of the data and report may be restricting. Therefore figures obtained from the Collaborating Centre may be different from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data and particularly those based on comparisons between pharmaceutical products, may be misleading. The information tabulated in the accompanying printouts is not homogeneous with respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. Some describe such information as "raw data". Any use of this information must take into account at least the above.

Some National Centres which have authorised release of their information strongly recommend that anyone who intends to use it should contact them for interpretation.

Any publication, in whole or in part, of the obtained information must have published with it a statement:

(i) of the source of the information,

(ii) that the information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction,

(iii) that the information does not represent the opinion of the World Health Organization.

Omission of these 3 statements may exclude the responsible person or organization from further information from the system.

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