Multiple chemical sensitivity seen from physiological and genetic properties of human populations affected by chemical stress

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Abstract

Introduction

Chemical-induced diseases are medical conditions of concern. The reasons why some patients develop clinical symptoms due to low-dose background exposure are completely unknown. This leads to an increased error ratio of individuals with „chemical-related symptoms" (CRS) to be patients of a psychiatric or any other disease.

Methods

1.143 (41.6 percent) of all 2.746 patients (visitors of my practise in Hamburg) between January 2000 and December 2003 answered a validated questionnaire about chemical symptoms called "modified QEESI". The primary aim was the measurement and documentation of the scores of the first ten items named "sensitizing capabilities of chemicals" (SCC). Then - without any medical information - the molecularbiologist Dr. Eckart Schnakenberg (university of Bremen, director of the "Institute for Pharmacogenetics and Genetic Disposition" - IPGD) analyzed the gene variants of the enzymes N-acetyltransferase 2, glutathione S-transferase M1, glutathione S-transferase T1. The single nucleotide polymorphisms of these genes of phase II in xenobiotic metabolism was analysed for 861 patients. After exclusion because age <20 years or age >90 years, psychiatrical and/or neurological diseases and ethnical causes remained 800 caucasian individuals for the case-control-study.

Results

The single nucleotide polymorphisms of these genes and the eight possible gene variants combinations - because of dichotomy of the phenotypes of enzymes - correlated significantly with the reported sensitizing capability of chemicals ($F=30.52$; $p < 0.000$). The modification of the SCC through gene variants was seen in people with no chemical exposure (exposure in background). After chemical exposure - measured by biomonitoring and/or ambiente monitoring - the SCC effects were stronger.

Conclusion

The observations give evidence that single nucleotide polymorphisms within these genes contribute to an individual risk for the development of chemical-related symptoms. However, these results can help to identify genetic influences in patients suffering from chemical-related symptoms and reduce the number of misclassified patients. In a political way the findings may modify the sustainability-strategy and plans of the evaluation of chemicals in the REACH process of the European Union.

Key words: questionnaire, sensitizing capability of chemicals, chemical-related symptoms, multiple chemical sensitivity syndrome, background exposure, susceptibility, single nucleotide polymorphism, gene variants

Abbreviations:

CRS	Chemical related symptoms
CYP1A1	cytochrome 1A1
CYP1A2	cytochrome 1A2
CYP2D6	cytochrome 2D6
GSTM1	glutathione S-transferase M1
GSTP1	glutathione S-transferase P1
GSTT1	glutathione S-transferase T1
MCS	multiple chemical sensitivity syndrome
NAT2	N-acetyltransferase 2
PCR	polymerase chain reaction
PON1	paraoxonase 1
QEESI	quick environmental exposure and sensitivity inventory

RFLP	restriction fragment length polymorphism
SCC	sensitizing capability of chemicals
SCE	sister chromatid exchange
SNP	single nucleotide polymorphism

Introduction

Chemical-induced diseases are a clinical entity of unknown origin. For more than hundred years it has been observed that chemicals like drugs and occupationally used substances may induce severe side reactions in human beings. Rehn was the first scientist who described in 1895 the importance of occupationally used chemicals as aetiological factors involved in the development of urogenital tract tumors (Rehn 1895). He identified the frequently used chemical substance aniline for releasing bladder cancer. Later the contamination of aniline by 2-naphthylamine was identified as risk factor for the development of bladder cancer. Another crucial experience happened in 1955 when Hughes et al. described adverse drug reactions after therapy of tuberculosis patients using isonicotinic acid hydrazide (Hughes et al. 1955). In this time N-acetylation was identified to be responsible for individual drug response making it possible to differentiate between slow and rapid acetylators.

Exposure to toxins like dioxin and other environmental chemicals have been shown to be metabolized by enzymes of phase I and/or phase II genes. In 1993 it was published by an expert team of the World Health Organization (WHO) that these enzymes are '*biomarkers of susceptibility… which may increase or decrease an individual's risk of developing a toxic response following exposure to an environmental agent. Polymorphism is present for some metabolic activation/deactivation enzymes, including cytochrome P-450 isozymes and at least one form of glutathione transferase. Differing rates of enzyme activity controlling the activation or detoxification of xenobiotics lead to differences in susceptibility by increasing or decreasing the biologically effective dose of the environmental agent*' (WHO 1993).

In addition to cytochrome P450 and glutathione S-transferase the metabolic polymorphism of the N-acetyltransferase after low-level environmental exposure to carcinogens has been described to be genetically based (Vineis et al. 1994). Furthermore, several other phase II enzymes of the glutathione S-transferases have been reported to be involved in the detoxification of chemicals (Hallier et al. 1993; Hayes et al. 2000; Seidegard et al. 1997) which are able to modify the individual disposition to diseases of human beings. Taking all these observations together it is becoming obvious that genetic factors may influence the disposition for the development of chemical-induced syndromes like multiple chemical sensitivity syndromes (MCS).

According to Cullen (1987) the following criteria were used to definate the symptoms of multiple chemical sensitivity syndromes (MCS) (Table 1):

MCS-Criteria (Cullen 1987)
· it is acquired after a specific health event in association with an environmental exposure
· symptoms involve more than one organ system
· symptoms recur and abate in response to predictable stimuli
· symptoms are elicited by exposure to chemicals of diverse classes and modes of action
· symptoms occur in response to very low levels of chemicals
· no widely available test of organ system function can explain the symptoms.

Table 1 MCS-Criteria

The prevalences of multiple chemical sensitivities in different populations are yet unknown. In a random sampling of 1.582 individuals from the Atlanta (Georgia) Caress and Steineman (2003) studied the prevalence of multiple chemical sensitivities (MCS). They reported the hypersensitivity to common chemicals in 13.5% of the sample. They remarked that technological progresses within the last ten years have made it possible to introduce rapid and reliable tests for genotyping i.e. in the area of pharmacogenetic approaches (Weber 2001; Schmitz et al. 2001).

A wide number of single nucleotide polymorphisms (SNPs) in the human genome has been identified so far. Several of these SNPs are located within phase I and phase II genes leading to an altered enzyme activity. The investigation of chemical-induced diseases is of importance because epidemiological studies have indicated that most human cancers are originally caused by long-term exposure to genotoxic agents. According to Doll and Peto (1981), 80 to 90 % of all cancers are related to environmental factors, tobacco smoke and diet. It is increasingly obvious that genetic differences among individuals in the ability to metabolize carcinogens like polycyclic aromatic hydrocarbons, aromatic amines, and nitroso compounds may play a primary role concerning the susceptibility to develop serious diseases like cancer (Idle 1991; Nebert 1991). The knowledge about the genetic relevance of metabolic variability has revealed new possibilities for studies focusing on increased susceptibility to environmental caused cancer and other environmental-influenced diseases.

Materials and Methods

The concept of this study was approved by the local ethic commission after pilot studies (Fabig 2000; 2002) to validate a questionaire for self reported sensitivites, which was developed by Miller and Prihoda (1999). This questionnaire is a standardized approach for measuring chemical intolerances for research and clinical applications named QEESI (quick environmental exposure and sensitivity inventory). All patients since Jan. 2000 - at the date 31.12.2003 2.746 individuals - were offered to answer this questionnaire. The modified QEESI contains - like the US-original - fifty items about quality, intensity, duration, localisation and modification of symptoms associated with environmental chemical exposure.

1.143 individuals answered this questionnaire without any medical influence or assistance. One focus in this study was to analyze the scores of the QEESI-items, in which the individuals evaluate their feelings of the “sensitizing capabilities of chemicals” (Table 2):

Please indicate whether or not these odors or exposures would make you feel sick …	**Not at all a problem (0)**	**Moderate symptoms (1)**	**Disabling symptoms (2)**
1. Diesel or gas engine exhaust			
2. Tobacco smoke			
3. Insecticide			
4. Gasoline			
5. Paint or paint thinner			
6. Cleaning products such as desinfectants, bleach, bathroom cleaners or floor cleaners			
7. Certain perfumes, air fresheners or other fragances			
8. Fresh tar or asphalt			
9. Nailpolish, nailpolish remover, or hairspray			
10. New furnishings such as new carpeting, a new soft plastik shower curtain or the interior of a new car			

Table 2 The items and score conditions to measure the sensitizing capabilities of chemicals (SCC)

The chemical relatetd symptoms (CRS) of the patients were head-related, muscle-related, neuromuscular, cognitive, gastrointestinal etc. (Table 3). The summaries of the CRS-scores of each

individual fluctuate – analog to the SCC-Scores - from zero (=no symptoms) to 20 points (=maximum of symptoms) were not shown in a later study.

Chemical-related symptoms (CRS)
1. Musculoskeletal
2. Airway-related
3. Heart/chest-related
4. Gastrointestinal
5. Cognitive
6. Affective
7. Neuromuscular
8. Head-related
9. Skin-related
10. Mucous membrane-related

Table 3 Chemical related symptoms (CRS)

861 of 1.143 persons gave an informed consent for genotyping enzymes of phase I and phase II in their xenobiotic metabolism. EDTA blood was sent to the molecularbiologist, who isolated DNA from EDTA blood as described by Lahiri and Nürnberger (1991) or using QIAamp DNA Blood Mini Kit. Genotyping was performed in all patients at N-acetyltransferase 2 (NAT2), glutathione S-transferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1). Dr. E. Schnakenberg described his part as followed (personal communication): "*After DNA extraction the N-acetyltransferase 2 gene was amplified as described previously (Schnakenberg et al. 2000). The single nucleotide polymorphisms (SNPs) nt 481, nt 590 and nt 857 of N-acetyltransferase gene were analysed in all individuals using RFLP or real-time PCR. According to the nomenclature of Vatsis et al. (1995) a simplified allele model was developed. The single nucleotide polymorphism nt 481 is a leading mutation which reflects the alleles NAT2*5A and NAT2*5B. The rare allele NAT2*5C was not identified by this procedure. These single nucleotide polymorphisms lead to a 4-allele model of the NAT2 which can predict the acetylator phenotype with an accuracy of more than 95 % for slow and rapid acetylation (Blum et al. 1991.)*

The detection of the deletion of glutathione S-transferase gene M1 and/or T1 was performed by multiplex-PCR as described previously".

The main substrates and the abbreviations (used symbols in this study) of the gene variants are shown in table 4.

NAT 2	GSTM1	GSTT1
Typ. Substrate: Benzidine	Typ. Substrate: Benz(a)pyrene	Typ. Substrate: Dichlorethane
substrate group: aromatic amines	Substrate group: analoge substrates	Subtrate group: Mono-Di- Halo-methane
used symbols of gene variants		
N0 : Slow acetylator	**M0** : GSTM1- gene deficience	**T0** : GSTT1- gene deficience
N1 : Rapid acetylator	**M1** : GSTM1-reference-sequenz	**T1** : GSTT1- reference-sequenz

Table 4 Main substrates and used abbreviations of the studied gene variants

343 individuals, which answered the questionnaire and 61 individuals with genotyping were excluded from the study, because they were either no caucasians or at ages < 20 or > 90 years, or had a history of psychiatric and/or neurologic disease, which may be accused as a confounder in studying MCS.

Data and statistical analysis

Statistics were performed using the SPSS software version 10.0. Calculation of odds ratios with a confidence interval of 95 % was performed to analyse the associations between self-reported chemical sensitivity and single nucleotide polymorphisms. To assess the significance of associations Pearson correlation (chi square), Fisher's exact test and logistic regression were used.

Results

Demographic data

The study group consists of 447 (56%) female and 353 male individuals. Age data show a plateau at the age from 40 to 70 years. The mean age was 52.1 (± 14.6) and the median 52.6 years. The age groups and genders differed not significant (Chi-Quadrat-Test 0.07; figure 1).

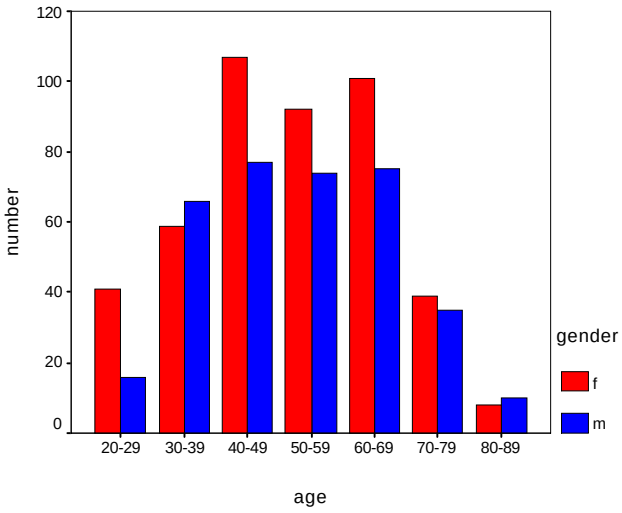

Figure 1 age groups and gender (N=800)

Genotyped data

Frequencies of genotyping the NAT2, GSTM1 and GSTT1 are shown in table 5.

NAT 2 - rapid	N	percent	NAT2 - slow	N	percent
4/4	71	8.9	5/5	168	21.0
4/5	161	20.1	5/6	217	27.1
4/6	94	11.8	5/7	12	1.5
4/7	9	1.1	6/6	64	8.0
			6/7	4	0.5
rapid N-acetylator	335	41.9	slow N-acetylator	465	58.1
GSTM1 *1/*1	380	47.5	GSTM1 *0/*0	420	52.5
GSTT1 *1/*1	664	83.0	GSTT1 *0/*0	136	17.0

Table 5 Frequencies of NAT2-, GSTM1- and GSTT1-gene variants

- The prevalence of slow N-acetylators in a reference-study of Cascorbi (et al. 1995) in Germany was 58.9%. In accordance to these findings the frequency of slow acetylators in the present study was 58.1%.

- GSTM1 gene deficience was detected in 53.5% of 416 white people of the US (Chen 1996). found this In the present study genotype GSTM1 *0/*0 was found in the prevalence 52.2 percent.
- Bruhn (et al. 1998) reported in a reference study (140 germans without illness) the deficience of the GSTT1 gene in 19.3 percent of all cases. Smaller frequencies of this genotype were analyzed in white US-Americans: 14.7 percent by Wourmhoudt (1999). In the current study frequency of GSTT1-Non-Conjugators was 17.0 percent.

Summerizing these results one can say that the study group is a very representative collective under the aim of studying the frequencies of these gene variants (Hirvonen 1993). Therefore also the arithmetic combinations of these gene variants are representative for Caucasians (table 6).

Combinations of gene variants	N	percent
N1*M1*T1	138	17.3
N1*M1*T0	23	2.9
N1*M0*T1	144	18.0
N1*M0*T0	30	3.8
N0*M1*T1	181	22.6
N0*M0*T1	202	25.3
N0*M1*T0	39	4.9
N0*M0*T0	43	5.4

Table 6 Frequencies of combinations of NAT2-, GSTM1- and GSTT1-gene variants (N=800)

Psychometric data

Figure 2 shows the frequencies of the sum scores of the reported sensitizing capabilities of chemicals (SCC) the . The individual minimum score was zero (= not at all a problem by chemical sensitizing), the individual maximum was a sum score of 20 points (=severe sensitizing by all of the asked chemicals). The mean of all SCC scores was 9.5 points (± 5.6).

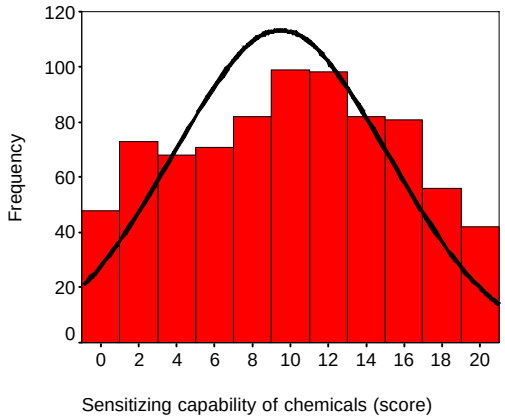

Figure 2 Frequency of sum scores of sensiziting capabilities of chemicals (N=800)

The mean of the female SCC scores was 10.2 (± 5.6), the median 10.0. Male had a non significant lower mean 8.6 (± 5.6) and a median of 9.0 (figure 3).

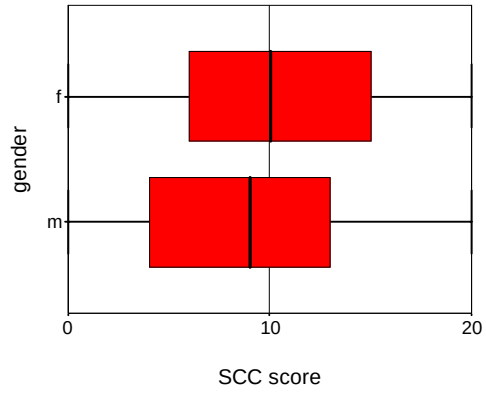

Figure 3 Gender and SCC-Scores

The generations lower than 40 years reported a lower capability of sensitizing by chemicals. The elderly (more than 70 years) did also. The linear regression of the SCC score with the body mass index showed no correlation (R=0.006). Non-smokers reported higher SCC scores than nicotine user (SCC mean 7.8 ± 5.1; median 8.0). They seemed to be more sensitive than smoker (SCC mean 10.3 ± 5.7; median 10.0; figure 4).

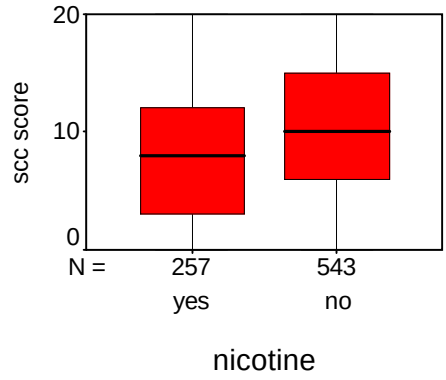

Figure 4 nicotine user and SCC scores (N=800)

Sensitizing chemical or mixture	Not at all a problem	Moderate symptoms	Disabling symptoms
1. Diesel or gas engine exhaust	188	403	209
2. Tobacco smoke	180	397	223
3. Insecticide	258	334	208
4. Gasoline	196	377	227
5. Paint or paint thinner	143	343	314
6. Cleaning products such as desinfectants, bleach, bathroom cleaners or floor cleaners	292	346	162
7. Certain perfumes, air fresheners or other fragances	257	340	203
8. Fresh tar or asphalt	328	339	133
9. Nailpolish, nailpolish remover, or hairspray	253	355	192
10. New furnishings such as new carpeting, a new soft plastik shower curtain or the interior of a new car	351	287	162

Table 7 Sensitizing chemicals and answers (N=800)

How the 800 sum scores of the reported sensitizing capabilities of chemicals were related to the preformed classification MCS or not MCS (Cullen`s criteria) were analyzed with logistic regression.

The results (numbers and percents) were shown in table 8.

		Predicted	
Observed			
MCS		No MCS	Percent correct
MCS			
	365	45	89.0
No MCS			
	49	341	87.4
total			
			88.3

Table 8 Results of logistic regression combining MCS and SCC scores (N=800)

The sensitivity of using SCC scores in detecting MCS was 89.0 percent. The specifity of SCC-method was 87.4 percent. In the ROC (Receiver Operating Characteristics) curve sensivity and specifity were combined (figure 5).

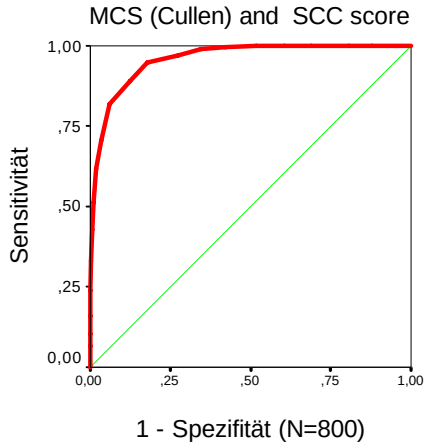

Figure 5 MCS (Cullen`s criteria) and SCC score from modified QEESI (N=800)

Case control by combining the genotyped and the psychometric data

The relations between the dichotomizing SNPs and the graduations in the questionnaires were analysed after excluding the answer “moderate symptoms”. The cases were 800 individuals with the answer “diasabling symptoms” from contacted chemicals. The controls were randomized from the whole study group. The results in relations to NAT2, GSTM1 and GSTT1 variants are shown in the tables 9a, 9b and 9c.

N-acetyltransferase gene variants	Disabling symptoms			Not at all a problem			slow acetylator	
Sensitizing chemical or mixture	**N0**	**N1**	**sum**	**N0**	**N1**	**sum**	**OR**	**95%-CI**
1. Diesel or gas engine exhaust	137	72	209	40	59	99	2.8	1.7-4.7
2. Tobacco smoke	150	73	223	40	56	96	2.9	1.7-4.9
3. Insecticide	148	60	208	48	77	125	3.9	2.4-6.5
4. Gasoline	151	76	227	36	61	97	3.8	2.0-5,.7
5. Paint or paint thinner	209	105	314	31	43	74	2.7	1.6-4.8
6. Cleaning products such as desinfectants, bleach, bathroom cleaners or floor cleaners	113	49	162	65	84	149	5.3	3.3-8.5
7. Certain perfumes, air fresheners or other fragances	139	64	203	62	77	139	2.7	1.7-4.3
8. Fresh tar or asphalt	89	44	133	68	98	166	2.9	1.8-4.8
9. Nailpolish, nailpolish remover, or hairspray	129	63	192	53	75	128	2.9	1.8-4.7
10. New furnishings such as new carpeting, a new soft plastik shower curtain or the interior of a new car	111	51	162	90	101	191	4.6	3.0-7.0

Table 9a NAT2 and sensitizing by chemicals. Number of cases, randomized controls and OR.

Glutathion-S-transferase M1 gene variants	Disabling symptoms			Not at all a problem			GSTM1 *0/*0	
Sensitizing chemical or mixture	**N0**	**N1**	**sum**	**N0**	**N1**	**sum**	**OR**	**95%-CI**
1. Diesel or gas engine exhaust	141	68	209	32	67	99	4.3	2.5-7.5
2. Tobacco smoke	151	72	223	39	57	96	3.0	1.8-5.2
3. Insecticide	132	76	208	46	79	125	3.0	1.8-4.9
4. Gasoline	148	79	227	34	63	97	3.5	2.1-5.9
5. Paint or paint thinner	198	116	314	24	50	74	3.6	2.0-6.3
6. Cleaning products such as desinfectants, bleach, bathroom cleaners or floor cleaners	106	56	162	51	98	149	3.6	2.2-6.0
7. Certain perfumes, air fresheners or other fragances	136	67	203	54	85	139	3.2	2.0-5.1
8. Fresh tar or asphalt	90	43	133	61	105	166	5.7	3.5-9.4
9. Nailpolish, nailpolish remover, or hairspray	123	69	192	45	83	128	3.3	2.0-5.4

10. New furnishings such as new carpeting, a new soft plastik shower curtain or the interior of a new car	96	66	162	83	108	191	3.4	2.2-5.1

Table 9b GSTM1 and sensitizing by chemicals. Number of cases, randomized controls and OR.

Glutathion-S-transferase T1 gene variants	**Disabling symptoms**			**Not at all a problem**			**GSTT1 *0/*0**	
Sensitizing chemical or mixture	**N0**	**N1**	**sum**	**N0**	**N1**	**sum**	**OR**	**95%-CI**
1. Diesel or gas engine exhaust	59	150	209	4	95	99	9.3	3.1-31
2. Tobacco smoke	52	171	223	6	90	96	4.8	1.9-13
3. Insecticide	44	164	208	9	116	125	2.6	1.1-5.9
4. Gasoline	59	168	227	4	93	97	8.2	2.7-27
5. Paint or paint thinner	70	244	314	4	70	74	5.0	1.7-17
6. Cleaning products such as desinfectants, bleach, bathroom cleaners or floor cleaners	40	122	162	13	136	149	3.4	1.7-7.1
7. Certain perfumes, air fresheners or other fragances	43	160	203	10	129	139	3.5	1.6-7.7
8. Fresh tar or asphalt	32	101	133	18	148	166	2.6	1.3-5.1
9. Nailpolish, nailpolish remover, or hairspray	45	147	192	13	115	128	3.0	1.5-6.2
10. New furnishings such as new carpeting, a new soft plastik shower curtain or the interior of a new car	34	128	162	25	166	191	1.7	1.0-3.2

Table 9c GSTT1 and sensitizing by chemicals. Number of cases, randomized controls and OR.

Table 10 shows gene variants, cases with SCC 10-20 or SCC 0-9 and odds ratios in individuals without reference-sequence gene variants after randomizing the group of controls.

Phase II genes with 2 SNPs	**SCC score group 10-20**			**SCC- score group 0-9**			**Non-reference-sequence variant**	
NAT2	N0	N1	sum	N0	N1	sum	OR	95%-CI
	291	124	415	104	108	212	2.4	1.7-3.9
GSTM1	M0	M1	sum	M0	M1	sum	OR	95%-CI
	283	132	415	74	138	212	4.0	2.8-5.8
GSTT1	T0	T1	sum	T0	T1	sum	OR	95%-CI
	91	324	415	29	183	212	1.8	1.1-2.9

Table 10 Hypersensitivities (odds ratios) in individuals without reference-sequence gene variants.

All three odd ratios were higher than 1.0 and their 95% confidence intervalles included never 1.0.

These data are shown in figure 6.

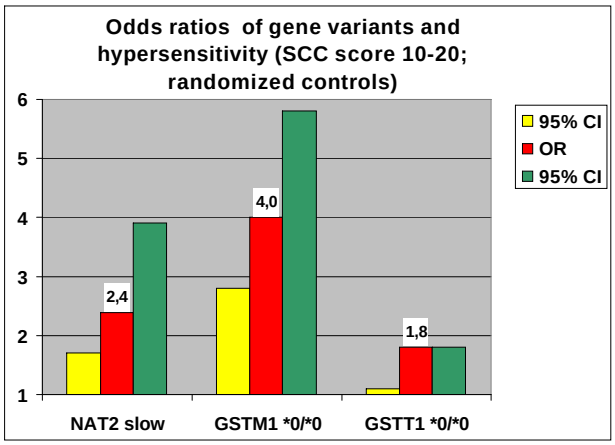

Figure 6 Odds ratios of hypersensitivity by chemicals in individuals with either slow N-acetylisation or GSTM1- or GSTT1- genotype *0/*0.

The means of 800 SCC scores in relation to the combinations of the eight gene variants were shown in figure 7.

Figure 7 Combinations of gene variants and means of SCC scores (N=800)

The chemical sensitivity had the lowest score, when gene variants of the reference sequences were combined individuals. The sensitivities had the highest score , when the non reference sequence genotypes were combined. The GSTT1 genotype *0/*0 seemed to be connected with the more sensitive individuals (in background).

Medians and quartiles of the SCC score in relation to the combinations of gene variants demonstrate a similar picture (figure 8).

Figure 8 SCC scores (box&whiskers) and combinations of gene variants (N=800)

The prevalence of hypersensitivity in the background was 18.4 percent, hypersensitivity following elevated exposure was 32.9% (Chi-Quadrat $p < 0.000$). 15.6% of the exposed were not sensitive against chemicals. 33.1 percent of the study group was neither exposed nor sensitive.

		Exposure		
Hypersensitivity		**elevated**	**background**	**sum**
yes	N	263	147	410
	% of 800	32.9	18.4	51.3
no	N	125	265	390
	% of 800	15.6	33.1	48.8
sum	N	388	412	800
	% of 800	48.5	51.5	

Table 11 Numbers and prevalences of exposures und sensitivities (N=800)

Conclusion

Hypersensitivities are caused by present or past exposure to chemicals either in the background or in special situations or conditions. A case control group with 800 individuals reported individual different sensitivities and documented the„sensitizing capabilities of chemicals " (SCC). 2400 gene variants of NAT2, GSTM1 and GSTT1, which seemed to be probably three of the most important genes in xenobiotic metabolism, were genotyped.

The results show different susceptibilities respect. their outcome different sensitivities, which are caused by different specific genetic properties. The highest odds ratio of hypersensitivity (higher SCC score) was related to GSTM1 genotype *0/*0 (OR 4.0). OR of GSTT1 genotype *0/*0 was 1.8 (1.1-2.9). Risk of slow N-acetylators was 2.4 (1.7-3.9). Current (unpublished) data show that also the SNPs of the genes Paraoxonase 1 (PON1), Epoxidhydrolase (mEH) and Cytochromes (CYPs) etc. are contributing factors in chemical sensitivities.

But gene variants respective SNPs are not the sufficient cause of hypersensitivity. Gene variants are contributing aetiologic factors, which only modify the toxic effects of exposures. Elevated exposed people in the study had a prevalence of hypersensitivity of 32.9 percent. Prevalence of hypersensitivity in background exposed individuals was 18.4 percent.

The analysed gene variants have - according to the analoge structures studied in pharmacogenetics - an evolutionary relatively stable position. In former times they were generated to metabolize toxicities and biochemics in nature life. Living creatures in the last centuries or decades were more and more stressed by multiple anthrogenic substrates. It seems alarming, that individuals in a common environment with "normal background" exposure and without diseases report more sensitizing effects of chemicals, if they own certain combinations of only three gene variants. Therefore seems that REACH must not only regulate and evaluate the CMR substances (carcinogenic, mutagenic and reprotoxic) and the substances with POP characteristics (persistent organic pollutants) but also must establish the conditions of specific permission (authorisation) of all chemicals. In addition we need characterizing the neurotoxic properties of lipophilic substrates, who are risk factors for developing toxic enzephalopathy (TE). The risk for TE in solvent exposed men was elevated in the cases of GSTM1 gene deficience (Soderkvist 1996)

Understanding hypersensitivity probably as a unwanted product of former economics and risk managements the European REACH process needs the framework of genotyping and analyzing the sensitizing capabilities of chemicals, before Multiple Chemical Sensitivity Syndromes (MCS) grow from handicaps to diseases.

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