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Subjective and objective signs of organic solvent toxicity among occupationally exposed workers

An experimental evaluation

by Anders Iregren, PhD¹

IREGREN A. Subjective and objective signs of organic solvent toxicity among occupationally exposed workers: An experimental evaluation. *Scand J Work Environ Health* 12 (1986) 469–475. A questionnaire consisting of 55 items concerning acute and long-term symptoms associated with exposure to organic solvents, as well as questions about type and duration of exposure, was distributed to 225 male spray painters in the Stockholm region. From the 152 respondents, two extreme groups were selected on the basis of frequency of solvent-related symptoms. Subjects for the experimental study ($N = 26$) were chosen from these groups and matched with respect to age and number of years employed as a painter. The subjects were experimentally exposed for 4 h to 3.2 mmol/m^3 (300 mg/m^3) of toluene and a control condition in an exposure chamber. Effects on performance were assessed with a computerized battery of four tests. Ratings of acute symptoms were also studied, and toluene exposure was found to affect them. However, there were no indications of toluene effects on performance, nor was there any correlation between symptom frequencies and performance levels. The only difference found between the two groups was a higher frequency of symptoms of local irritation in the group which had reported high symptom frequencies on the questionnaire.

Key terms: experimental exposure, performance tests, reaction time, spray painters, symptoms, toluene.

During the last decade a number of cross-sectional epidemiologic studies has indicated lowered performance capacity in different groups of workers with low-level occupational exposure to organic solvent mixtures as compared to unexposed groups. In two studies of house painters (10, 14), the performance of the painter group was inferior to that of a reference group. Similar results have been found in two investigations of spray painters (6, 9). In these studies, effects on performance were demonstrated, although the exposure levels were not considered to have been above current industrial exposure limits. Thus, on the basis of performance decrements found in several different groups of workers with low-level long-term exposure to solvent mixtures, the adequacy of the present exposure limits has been questioned.

In spite of this apparent inadequacy of the limits, several recent experimental exposure studies on human subjects using common solvents have either failed to find effects or found only small effects of exposure to concentrations close to the present exposure limits. This was the case with two of the most commonly used solvents, ie, toluene and xylene, which were studied by Iregren et al (12) and Anshelm Olson et al (2). In these experiments only marginal effects on subjective symptoms like headache and local irritation were found

after 4 h of exposure to toluene and xylene at the level of the Swedish exposure limits, ie, 3.2 mmol/m^3 (300 mg/m^3) and 3.3 mmol/m^3 (350 mg/m^3), respectively. In three other studies of toluene exposure, Andersen et al (1), Baelum et al (3) and Dick et al (5), subjects were exposed to 100 ppm, ie, approximately 4.1 mmol/m^3 or 375 mg/m^3 , for 6, 6, and 4 h, respectively, and these studies also showed only small or ambiguous effects.

A common criticism of this type of experiment concerns the choice of the subjects participating in the studies. For practical reasons only a very limited number of subjects can be studied in each experiment, and generally these subjects have been recruited among students or the employees at the institute performing the study. Thus most of the available experimental data on effects of organic solvent exposure derive from highly select groups of healthy, young men. It is possible that there is a difference in susceptibility to the toxic effects of solvents between these groups and, eg, a painter population, in which case the choice of subjects may have resulted in a decreased sensitivity in this type of investigation (7).

Another reason for questioning the current exposure limits has been the fact that differences in susceptibility may also exist within a group of workers, due to individual characteristics. In the case of allergic reactions, it is evident that the pronounced sensitivity makes it more or less impossible to remain in the profession. Disregarding these cases, it still seems plausible that there is a rather wide range in susceptibility to the toxic effects of solvent exposure, eg, within a

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painter population. One possible indicator of such differences in susceptibility could be symptoms as reported by the subjects, although it is not known to what extent subjective symptoms are early predictors of long-term effects.

The present investigation was carried out on a group of occupationally exposed spray painters to study the possible correlations between susceptibility to the toxic effects of organic solvent exposure, as measured by reported symptoms, and performance capability, as measured in the laboratory during controlled exposure.

Subjects and methods

Symptom survey

With the assistance of the Painters Union and the Metal Workers Union a large group of spray painters was identified, which included the majority of the spray painters in the Stockholm region. The workers were located through the member register of the Painters Union, and through the local organization of the Metal Workers Union at the 15 largest enterprises with painting departments within this area.

A postal questionnaire together with adequate information was sent to the male spray painters under 65 years of age in the Painters Union, a group of 153 people. The painters belonging to the Metal Workers Union were given the questionnaire personally by a board member of the local union, and 72 questionnaires were distributed in this way. Thus, a total of 225 male spray painters were included in the symptom survey. Those who had not returned the questionnaire within two weeks were reminded with a further copy, and a total of 152 questionnaires were returned within four weeks. Thus the response frequency was 67.6 %.

The questionnaire was constructed for the assessment of symptoms of solvent exposure, as well as for gathering background data concerning employment and exposure times. The symptom-related questions were divided into two parts, one regarding acute effects and one concerned with suspected long-term effects of solvents. The specific items were chosen according to previous experience from investigations of long-term exposure to organic solvents (4, 6, 11), from experimental laboratory investigations of acute effects (1, 2, 12), and from an ongoing prospective study of workers engaged in the production and distribution of electricity (8). The questions on long-term effects covered, eg, symptoms pertaining to the autonomic nervous system, concentration deficits, fatigue, tiredness, dizziness, and symptoms of peripheral neuropathy. A number of questions referring to general somatic symptoms was also included. Altogether 38 questions regarding symptoms experienced during the last six months were included. For each question the subject indicated on a four-point scale whether he had felt the symptom "very often," "rather

often," "sometimes," or "never." Subjects were also asked to indicate for each symptom whether they considered it related to solvent exposure at work or not.

The items concerning acute effects covered aspects like headache, dizziness, tiredness, nausea, and local irritation of the skin, eyes and mucous membranes of the airways. A total of 17 questions regarding acute effects were included. The ratings of acute symptoms were also made on a four-point scale, on which subjects rated to what extent they had experienced the different symptoms. The categories were labeled "quite a lot," "a little," "negligibly," and "not at all."

Furthermore, questions were asked as to the duration of employment in exposed work and the use of protective garments at the worksites. The subjects were also asked about their present use of pharmaceuticals, and whether they considered themselves more or less affected by solvents than their colleagues. A question regarding possible changes in the sensitivity to solvent effects was also included.

In an attempt to determine the relational structure of the items of the questionnaire, the symptom data from the 152 questionnaires returned within four weeks were subjected to a factor analysis. The 38 items concerning symptoms experienced during the last six months were included in the analysis, together with the 17 questions regarding acute symptoms experienced after a normal workday. The method used was a principal factor analysis with varimax rotation, and a three-factor solution was found satisfactory. Items representing a factor were chosen according to the criteria that the items should have a loading of at least 0.40 in the factor and there should be a difference of at least 0.20 between the highest and the second highest loading.

Symptoms pertaining to the autonomic nervous system and symptoms like aching back, pain in the hands and joints, and feelings of losing consciousness loaded on the first factor. This factor, which was defined by 13 items, will be referred to as the "somatic symptoms" factor. Most of the symptoms loading on this factor have not been ascribed to solvent exposure. Twelve items concerning tiredness and fatigue, as well as concentration difficulties and headache, were found to load on the second factor, which will be referred to as the "neurasthenic symptoms" factor. Finally, 14 items relating to symptoms of local irritation, in the eyes and the airways, as well as of the skin, loaded on the third factor, which will be referred to as the "irritation symptoms" factor. The types of symptoms loading on the neurasthenic and irritation factors have generally been considered to be related to solvent exposure (6, 11). A total of 16 items showed ambiguous factor loadings and were thus not used in the selection of the subjects.

Selection of subjects

After exclusion of the painters with some form of pension, all the painters who were not presently employed

as spray painters, all persons on medication for some type of chronic illness, and also immigrants from all countries except Denmark, Finland, and Norway, the resulting group consisted of 122 persons. On the basis of the results of the factor analysis three indices were calculated for each of these painters, one index relating to each factor. These indices were the number of symptoms experienced by each subject. The 122 spray painters were then ranked according to their scores for the two indices based on the neurasthenic symptoms and irritation symptoms factors.

A pairwise matching was made according to age and duration of exposure among the 25 highest and the 25 lowest ranking painters. Two subjects with no symptoms related to the somatic symptoms factor were excluded from the insensitive group. This exclusion was made to reduce the risk of bias from symptom ratings by denial. Matching was possible for 42 spray painters; thus the two extreme groups with regard to subjectively reported sensitivity to solvent exposure were reduced to 21 persons each. Every painter selected was personally contacted and invited to participate in the subsequent experimental exposure study.

The number of painters actually taking part in the experiment was further reduced by refusal to take part (12 cases), by exclusion on medical criteria (3 cases), and by the employer's refusal to allow absence from work (1 case). The number of subjects was thus reduced to 26, 12 of whom belonged to the insensitive group and 14 to the sensitive group. Data on age and exposure time for the two groups are presented in table 1, and the distributions of the symptom indices for the two groups are illustrated in figure 1.

Experimental design

In order to allow comparisons with earlier experiments, as few changes as possible were made from the design of the studies by Anshelm Olson et al (2) and Iregren et al (12).

The subjects were exposed to toluene at a concentration corresponding to the present Swedish exposure limit (3.2 mmol/m^3 , 300 mg/m^3) and to a control condition with exposure to 0.2 mmol/m^3 (approximately 20 mg/m^3) of toluene. Thus the subjects were used as their own controls in a repeated measurement design, and the interval between the two experimental days was one week. The exposure trials were performed on the same day of the week for each subject. Two subjects

at a time were studied in the exposure chamber, one belonging to the sensitive group and one belonging to the insensitive group. The order of the two exposure conditions was balanced within the groups.

The subjects were given a light standardized breakfast before entering the chamber, and directly upon entrance a base-line measurement was performed. The subjects then left the chamber for a short time while the proper atmosphere was generated. The exposure sessions lasted 4 h.

Performance capability was tested with a battery of four tests at three times within each exposure occasion. In addition to the base-line testing, measurements were made after 2 and after 3.5 h of exposure.

The subjects were given a medical examination on the day preceding the first exposure occasion. On the same day, they were given extensive information about the experiment. The subjects were informed about the maximal exposure level to be used, but they were not told the order of the exposure conditions, nor about the formation of two extreme groups with respect to sensitivity. On this occasion all the subjects trained by going through the test sequence twice, and they were carefully instructed in the use of the symptom rating scales.

Performance tests

The performance assessment was accomplished with a computerized battery of four tests, administered in the following order: choice reaction time (CRT), simple reaction time (SRT), color-word vigilance (CWV), and memory reproduction (MR). For a detailed description of the tests, see the report of Iregren et al (12).

The computerization permitted a fully automated testing process, in which the experimenter surveyed the procedure from outside the chamber. The equipment for each of the two subjects tested simultaneously included a microcomputer (ABC806, Luxor AB, Motala,

Table 1. Age, exposure time, and number of subjects for the selection group and the two experimental groups.

Group	N	Age (years)			Exposure (years)		
		Mean	SD	Range	Mean	SD	Range
Selection	122	36.4	12.1	19–64	14.3	11.4	0.5–45
Insensitive	12	34.7	12.1	20–60	13.2	11.4	0.5–31
Sensitive	14	36.1	10.7	19–64	12.0	9.2	1–35

Figure 1. Distribution of the different symptom indices in the two selected groups.

Sweden) with a dual disc drive, a printer, a reaction-time panel with adapter, an external millisecond clock, and a modified numerical keyboard (13).

During the exposure sessions the subjects were told via telephone to start a testing sequence, and the performance testing was totally self-administered. The printers were placed outside the chamber and used by the experimenter for surveillance of the procedure.

Acute symptom questionnaires

During a short interval between the second and the third performance test in each testing sequence the subjects completed two questionnaires concerning acute symptoms. One of these questionnaires contained the 17 questions relating to acute symptoms used in the symptom survey, and the other was identical to the symptom questions posed in the experiment by Iregren et al (12). On this second questionnaire the subjects rated the extent to which they experienced nausea, headache, or irritation in the eyes, nose, or respiratory tract using the following four response categories: not at all, negligibly, slightly, and quite considerably.

The subjects also rated their mood with respect to six different dimensions, ie, with respect to being "bored," "unable to concentrate," "stressed," "sleepy," "irritated," and "affected." The rating scales ranged from -10 (less than normally) to +10 (more than normally). For the dimension "affected" the scale ranged from 0 to +10.

Statistical evaluation

The performance data were subjected to analyses of variance (ANOVA). The model used was a three-factor model with independent groups in one factor (sensi-

tivity) and two factors with repeated measurements (exposure and time of day). As the first measurements each day were performed as base-line registrations before the onset of exposure, all calculations were performed on differences between the base-line and subsequent measurements. This model was adopted since a preliminary test for possible effects of the order of exposure conditions did not yield any performance differences. The symptom indices were subjected to the same type of analysis.

The graphic presentation of the results has been made in the form of Z diagrams. The standardized mean scores (ie, Z-values) were calculated according to the equation $Z = \pm (X_e - X_b)/S_b$, where X_e is the mean value of the result variable in the exposure condition, X_b is the mean value of the base-line measurement of the same day, and S_b is the standard deviation of the variable calculated over all the values from the base-line measurements. A negative value indicates a decrease in the severity or frequency of symptoms.

Results

Performance tests

No differences in performance due to exposure were found, nor were there any performance differences between the sensitive and insensitive groups. Table 2 presents the data from the four performance tests.

Furthermore, the performance levels were not found to correlate with the symptom frequencies reported in the survey, nor was there any association between the test results and the symptoms reported during the experimental exposure.

Table 2. Test performance of the two groups by exposure conditions and measurement occasions. (1 = base line, 2 = after 2 h of exposure, 3 = after 3.5 h of exposure)

Test/variable	Insensitive group						Sensitive group					
	Control			Exposure			Control			Exposure		
	1	2	3	1	2	3	1	2	3	1	2	3
Choice reaction time/ reaction time (ms)												
Mean	717	718	734	738	737	726	710	723	732	704	720	743
SD	98	84	86	133	118	83	107	97	99	108	106	108
Simple reaction time: level/reaction time (ms)												
Mean	258	261	264	260	264	271	251	249	263	259	272	277
SD	37	27	36	40	27	35	40	43	40	45	62	68
Simple reaction time/ variation												
Mean	59	75	75	63	77	78	50	63	78	58	78	78
SD	26	24	26	24	16	29	15	20	33	26	34	32
Color word vigilance test/reaction time (ms)												
Mean	505	525	519	521	530	533	533	499	509	513	522	511
SD	49	42	31	38	45	25	48	72	36	45	53	50
Memory reproduction/ elements												
Mean	43	46	44	43	44	45	42	44	43	42	43	43
SD	4.8	3.4	4.0	4.0	3.5	3.6	3.4	3.4	3.2	4.0	4.4	3.9

Symptoms

The acute symptom items rated during the exposure were divided into two groups, one relating to symptoms of the central nervous system (CNS), eg, headache, dizziness, and tiredness, and the other relating to symptoms of local irritation, as of the eyes, skin, and airways. For each group of symptoms an index was calculated as the number of symptoms showing an increased rating from the base line to the subsequent measurements.

The index of CNS symptoms was found to increase with exposure ($F_{1,24} = 16.58$, $p < 0.001$) and to decrease from the second to the third measurement during the sessions ($F_{1,24} = 7.56$, $p < 0.05$). The results

for this index, which are presented in figure 2, did not differentiate between the two groups. On the other hand, the index of symptoms of local irritation differed significantly between the sensitive and insensitive groups ($F_{1,24} = 7.81$, $p < 0.01$) and varied with exposure ($F_{1,24} = 13.76$, $p < 0.01$). The results for this index, which are presented in figure 3, did not differ between the second and third measurements. The symptom data are presented in table 3.

On the mood scale the subjects reported that they felt more affected under exposure conditions ($F_{1,24} = 8.73$, $p < 0.01$) than under control conditions, while there were no differences with regard to the other factors (ie, sensitivity and time of day).

Figure 2. Symptoms of the central nervous system (CNS). Differences in the index for CNS symptoms between the base-line measurements and subsequent measurements for the two exposure conditions and the two groups. The differences are expressed as standardized mean scores (ie, Z-values). See the Methods section for the calculation of the Z-values.

Figure 3. Symptoms of local irritation. Differences in the index for the local irritation symptoms between the base-line measurements and subsequent measurements for the two exposure conditions and the two groups. The differences are expressed as standardized mean scores (ie, Z-values). See the Methods section for the calculation of the Z-values.

Table 3. Symptom indices for the two groups by exposure conditions and measurement occasions. (1 = base line, 2 = after 2 h of exposure, 3 = after 3.5 h of exposure)

Symptom index	Insensitive group						Sensitive group					
	Control			Exposure			Control			Exposure		
	1	2	3	1	2	3	1	2	3	1	2	3
Symptoms of the central nervous system												
Mean	0.4	1.2	1.0	0.5	1.9	1.5	0.8	1.8	1.6	0.8	2.5	2.4
SD	0.5	0.9	0.7	0.5	0.9	1.0	0.8	1.0	0.8	0.8	1.2	1.3
Local irritation symptoms												
Mean	0.6	0.8	1.3	0.8	1.9	1.7	1.3	2.7	2.8	1.1	4.1	3.9
SD	1.2	0.6	1.0	1.1	1.2	1.2	1.5	1.3	1.4	1.4	2.0	2.7

Discussion

The purpose of this investigation was to study the possible correlations between effects on performance, as measured during controlled exposure, on one hand and differences in susceptibility to the effects of organic solvent exposure, as measured by reported symptoms, on the other. Thus the selection of subjects to the exposure experiment was crucial to the validity of the study.

The selection of the two extreme groups with respect to reported symptoms related to solvent exposure made it necessary to identify a large group of potential subjects. This group comprised 225 male spray painters in the Stockholm region. The representativity of this group, with respect to a population of spray painters, could be discussed, since the response frequency was not very high. This low frequency was probably due to the fact that information about the subsequent exposure study was given together with the questionnaire. Painters unwilling to take part in the experimental exposure could thus refrain from completing the questionnaire. This representativity is of less importance, however, as long as the within-group variation concerning reported symptoms is large. This was obviously the case in the group which answered the symptom questionnaire.

A factor analytical approach always implies some subjectivity regarding the interpretation. In this case, a three-factor solution was found satisfactory, since it was possible to interpret the three factors in accordance with the findings in earlier studies on solvent-related symptoms. Thus the questions concerning symptoms of local irritation caused by solvent exposure loaded on one factor, the solvent-related symptoms from the CNS loaded on a second factor, and the general somatic symptoms not usually ascribed to solvent exposure loaded on a third factor.

As can be seen from figure 1 the selection of the two groups was successful in that they were extremes with respect to the two solvent-related factors. The difference with respect to the somatic symptoms not related to solvent exposure was similar although not so consistent.

As to the result of the exposure experiment, there were no differences with respect to performance between the sensitive and insensitive painter groups. The previously reported symptoms were thus unrelated to performance capability. Nor were there any effects of exposure on performance, which is consistent with earlier findings (1, 2, 5, 12). Thus no differences in sensitivity between the occupationally exposed painters and the volunteers tested in earlier studies were indicated.

On superficial inspection our results do not agree with those recently reported by Bælum et al (3), who claim to have found adverse effects on performance after 6-h of exposure to 4.1 mmol/m³ (375 mg/m³) of

toluene. However, for several reasons their results are open to debate. The interpretation of the results of their study is complicated by problems with, eg, mass significance, the test variables (often error rates), and the inconsistency of exposure effects over the tested groups. Furthermore, the only test yielding consistent exposure effects in their study was a test of color discrimination, which is a test of sensory judgement and not a test of the kind of performance effects generally ascribed to solvent exposure.

The increase in reported symptoms during the exposure condition was the most consistent finding in our study. Thus on one questionnaire there was an increase both with respect to CNS symptoms and to symptoms of local irritation. There seemed to be some adaptation to the exposure effects since, for the CNS symptoms, there was a decrease from the second to the third measurement. The symptoms of local irritation showed a tendency to decrease during the day, and this decrease might also indicate some adaptation. These changes were similar in both the sensitive and the insensitive group. On the second questionnaire there was an increase with respect to feeling affected in the exposure condition, but no differences between the groups and no signs of adaptation.

One difference between the groups regarding reported symptoms was found. The sensitive subjects reported symptoms of local irritation twice as often as the subjects of the insensitive group. It might be argued that this difference was caused by the selection of subjects with a very low general tendency to report symptoms to the insensitive group. This explanation is not very probable, however, since the groups neither differed with respect to CNS symptoms nor showed any differences on the second questionnaire. Furthermore, two subjects were excluded from the insensitive group because of their denial of symptoms in the somatic symptoms factor. This was done to reduce the risk for the aforementioned bias. A more likely explanation would be that the selection process resulted in two groups which differed mainly with respect to sensitivity to local irritation.

Since the groups differed only with respect to symptoms of local irritation, it is conceivable that there could be a correlation with a mild tendency towards allergic reactions. To test this hypothesis, a more elaborate medical examination would have to be undertaken.

In conclusion, the present investigation failed to find a relation between the frequency of reported symptoms and measures of performance. Neither could the painters in this study be shown to react differently from volunteers in previous studies during controlled exposure. This result leads me to believe that exposure to toluene at the level of the present Swedish industrial exposure limit, ie, 3.2 mmol/m³ (300 mg/m³) does not constitute any tangible risk as regards acute effects on the psychophysiological performance of occupationally exposed workers.

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