Behavioral Methods and Organic Solvents: Questions and Consequences

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This paper reviews some illustrative examples of studies of human neurobehavioral effects from experimental as well as long-term occupational organic-solvent exposure. My objective is to present a selection of neurobehavioral solvent studies with the educational aim that we may hopefully learn from the early experiences of others. Some of the methodological problems encountered in these studies are discussed, as well as some reasons for the relative success of the work performed by certain Scandinavian research teams. — Environ Health Perspect 104 (Suppl 2):361–366 (1996)

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Introduction

Behavioral methods have frequently been used in the study of effects from exposure to organic solvents for some three decades, and there is an ever-increasing number of publications in this area of research. Today, the prenarcotic effects from acute solvent exposures are widely accepted, and even the central nervous system (CNS) effects from long-term low-level exposures are being increasingly acknowledged. However, this recognition, or acceptance, of the neurotoxicity of organic solvents has been obtained very slowly and following great struggle over the years.

This paper reviews some of the effort expended in the study of human neurobehavioral effects from organic-solvent exposure and summarizes the most important lessons that we could learn from previous studies. It should be stressed that the aim of this paper is by no means to provide an exhaustive review of investigations in this area but rather to present a selection of neurobehavioral solvent studies, with the educational aim that we may learn from the early experiences of others.

Brief History of Solvent Research

In the 1960s behavioral outcome measures were frequently used within pharmacology and were also occasionally applied to the study of possible effects from various environmental exposures. This was especially so in psychological research in Great Britain, where psychological performance had been studied extensively even during the 1950s.

One of the earliest efforts in the study of effects from organic-solvent exposure was that of R. D. Stewart, who, with his colleagues, published a series of studies on different solvents in the 1960s and 1970s (1–6). However, behavioral measures were applied only in some of these studies; even in those cases where such methods were applied, they were relatively crude clinical tests of gross functional capacities. Stewart's effort was also the first serious attempt to measure the behavioral outcome of acute exposures to different solvents in a systematic way.

In the late 1960s, workers and their unions in Swedish industry started to debate the possible health effects from organic-solvent exposure and to seriously question the use of organic solvents, at least with the very high exposure levels prevalent in those days. Eventually in Sweden this debate led to a major effort to study various effects from acute exposures to solvents. A long series of experimental studies was undertaken at the precursor to the Swedish INIOH in collaboration between researchers from several disciplines, including chemistry, medicine, physiology, and, last but not least, psychology. This was the series of studies in which Irma Åstrand and her co-workers (7) reported results regarding uptake, distribution, and elimination of the solvents, and Francesco Gambarelle and his co-workers (8–14) described effects on the CNS. In these experiments, human volunteers were exposed to the solvents toluene (8), methyl chloroform (9), styrene (10), methylene chloride (11), white spirit (12), trichloroethylene (13), xylene, and ethylbenzene (14) and the behavioral effects resulting from these exposures were studied.

Also during the late 1960s, H. Hänninen (15) at the IOH in Helsinki, Finland, began to study workers from a viscose rayon plant. These workers were exposed to CS₂; they exhibited numerous symptoms of disturbances to the CNS, which in some cases were quite severe. In 1971 Hänninen (15) reported on the first study of the behavioral consequences of CS₂ exposure.

In contrast to the studies by Stewart et al. (1–6), Åstrand (7), and Gambarelle (8–14), Hänninen's data concerned workers with chronic occupational exposure to the toxic agent. In many cases the exposure had lasted some 20 years or more. Thus, it was no surprise that the effects were generally not transient like those following acute exposures. On the contrary, the effects from long-term CS₂ exposure proved to be lasting and, in some cases, even worsened over the years to come.

Later on, Hänninen's group reported numerous studies on the behavioral effects from occupational exposures to other compounds, e.g., styrene (16), toluene (17), and solvent mixtures (18,19). A series of experimental studies on solvent exposure has also been performed by Riihimäki and his colleagues (20,21).

During the first half of the 1970s, Winneke and his colleagues [unpublished data; (22)] performed some experimental studies on the effects from acute exposure to solvents. The solvents investigated were...
methylen chloride (22), trichloroethylene, and toluene (Winneke et al., unpublished data). This group of researchers also studied behavioral effects from carbon monoxide, alcohol, and some pharmacological drugs using various psychological tests.

Questions Asked

Experimental Studies

At first, the simple question asked in the experimental studies on behavioral effects from organic solvents was "Are there behavioral effects from acute exposure to solvents?" Since neither traditional toxicological methods nor clinical observations could verify any effects from acute exposures at levels generally found in the workplace in the 1960s and 1970s, there was an intense debate on this issue. Thus, it was difficult for the workers and their trade unions to get any substantial support for their view that a reduction of the existing solvent-exposure levels was necessary. Therefore, the simple question for Stewart, Gambereale, and the other pioneers of solvent research was, "Are effects observed at the exposure levels generally found in the industry?" To the surprise of many, the answer was definitely "yes" for several of the most frequently used organic solvents.

For many of the solvents in these early experimental studies, it was possible to demonstrate not only effects per se but a dose–effect relationship between various environmental and biological measures of exposure and transient prenarcotic effects on performance in the behavioral tests applied (23). Still, numerous critics questioned the validity of the findings, indicating, for example, that results obtained under the artificial circumstances in the laboratory were not representative of the situation in the actual work environment.

Field Studies

Consequently, the next question asked was "Is it possible to replicate the laboratory findings on acute solvent exposure directly at the work sites?" To provide answers to this question, investigations that Gambereale (24) has labeled "quasi-experimental field studies" were performed directly at the work site in industries in which workers were exposed to organic solvents.

In these studies the general approach was to use a balanced study design to measure possible effects in exposed and nonexposed groups of workers before and after a normal workday. Our research group performed such studies with workers in the plastic boat industry who were exposed to styrene (25), workers in the steel industry exposed mainly to methyl ethyl ketone (MEK) (26), and workers in the paint manufacturing industry exposed to solvent mixtures (27).

The results obtained from these studies clearly indicated that effects similar to those observed in the laboratory could also be demonstrated directly in the workplace with exposure levels commonly found at that time in the industry. It was thus possible to verify and validate the laboratory findings on the CNS effects from acute laboratory exposure to organic solvents.

The experiments as well as the field studies address questions related to shortterm, i.e., acute, exposure. Most experiments have involved exposure for periods of a few hours up to (in some rare instances) several days, and field studies generally investigate effects of exposure during one workday. The relevance of results from these studies for the setting of occupational exposure limits (OELs) may be limited because these studies primarily deal with supposedly transient prenarcotic effects. No information is presently available on the relationship between these effects and longlasting effects on the CNS. More lasting effects have been indicated by numerous studies, mostly from Scandinavia, comparing various behavioral parameters in exposed and nonexposed groups of workers.

Cross-sectional Studies

In the studies where effects on performance and symptoms in groups have been compared, the common question is "Are there observable behavioral effects from longterm occupational solvent exposure in groups of workers?"

This is the type of study that Hänninen (15) reported in 1971 on workers exposed to CS$_2$. This is also the most frequently reported type of study of effects from organic-solvent exposure. Since the publication in 1971 by Hänninen (15), probably hundreds of cross-sectional studies have been performed by numerous groups of scientists, with varying results.

From a strictly theoretical point of view, this post-factum study design, by choosing subjects from already established populations and having no control over the exposure, makes it impossible to establish a cause–effect relationship. Thus, these studies, taken one by one, cannot prove that organic solvents are neurotoxic. However, when information from the large number of cross-sectional solvent studies is considered altogether, there is clearly quite strong evidence that many organic solvents and their mixtures are neurotoxic.

Studies comparing effects from chronic exposures in clinical groups are relatively common. As compared to the cross-sectional studies of active workers, the problem concerning the representativeness of the subjects is still of greater concern in clinical studies. This problem, of course, is related to the fact that there is a very important process of selection involved in studying patients; patients are selected because of the presence of pronounced symptoms or signs, and in many studies they are to a large extent self-selected.

In most studies of clinical groups, there are difficulties related to badly defined clinical entities, which are a consequence of the widespread and nonspecific effects of most solvents on the CNS. For some clinical studies, the problems have been related to the representativeness of the test norms (28).

Evaluating Behavioral Solvent Research

Several agencies in different countries have summarized the evidence for effects from numerous organic solvents in documents that serve as a basis for the regulation of the general environment or of the work environment specifically. Such documents have been prepared, e.g., by Dutch, Swedish, and U.S. agencies (29). The extent to which behavioral studies are taken into account in these reviews varies somewhat, but the willingness to acknowledge the importance of behavioral effects in the setting of exposure limits seems to be increasing. This is true, e.g., in Germany; in Sweden the regulatory authorities are asking for more data that relates to behavioral measures such as performance and to the perception of comfort.

Following the preparation of such criteria documents, the process of arriving at an actual exposure limit varies between countries (30).

In Sweden the generation of new or revised occupational exposure limits is a process of discussion in which government officials work together with representatives of employer and employee organizations (31). In this process, toxicological data, as well as technical and economical aspects, are taken into consideration; during recent years, quite extensive documents containing specific descriptions of consequences have resulted from these discussions. Thus, for the latest revisions of Swedish OELs, it is
possible to follow in detail the arguments that constituted the bases for decisions.

Research Problems

Preparation of a scientific criteria document, which provides a basis for the generation of OELs and summarizes reviews of the relevant literature, requires a thorough knowledge of the methodological problems involved in the research process and the ability to evaluate scientific reports. The handling of methodological difficulties may be crucial to the interpretation of the reported results. A brief discussion of some examples is given below.

Representatvity of Groups

The representatvity of the study groups is an essential issue in scientific research in general. Regardless of whether the study is carried out using volunteers in the laboratory or as a cross-sectional comparison among various groups of workers, the choice of subjects may severely limit the possibilities for generalization of the results. However, the possible problems with the selection of subjects vary with the choice of study design.

Experimental Studies. In the vast majority of laboratory experiments on the effects of acute solvent exposure in human subjects, students or employees at research institutions have been recruited as volunteers. The choice of such a select group of subjects may obviously limit the representatvity of results since the general population comprises more potentially sensitive groups, i.e., young children, pregnant women, and the elderly.

Some attempts at controlling this potential problem of representatvity in experimental studies have been made, e.g., by Iregren (32), who studied subjectively sensitive and insensitive spray painters during experimental toluene exposure, and Belum and colleagues (33), who studied occupationally exposed workers as well as volunteers from the general population. These two studies did not indicate any difficulties with the representatvity of the study groups, but very few studies attempting to address such problems have been published so far.

Field Studies. Because this study design is used in the workplace with actual workers, the problem of representatvity is not as large as in laboratory experiments. However, in a field study, the choice of a control group becomes essential since a number of possible confounding variables have to be controlled. Thus, with this design the main problem is to find a group that is not exposed to any neurotoxic compounds and is also comparable to the exposed group in as many relevant aspects as possible.

Cross-sectional Studies. For the cross-sectional study design, the problem of representatvity is similar to that encountered in the field study. Since there is no experimental control over exposure, the strict control of possible confounders becomes essential. There have been several examples of difficulties in the selection of control groups for cross-sectional studies, some of which were performed at the Swedish National Institute of Occupational Health (NIOH). The study by Knave et al. (34) on the effects of exposure to jet fuel is one example, in which the selection of the first control group proved to be biased, so the selection and testing of a second control group was necessary. Another example of this problem was the cross-sectional study of spray painters reported by Elofson and colleagues (35), in which the first control group proved to be severely negatively biased and had to be replaced by a new comparison group.

An elegant approach to solving the problem of representatvity of the control group was reported by Hänninen et al. (36), who studied pairs of monzygotic twins. In 17 pairs of twins they found that one was occupationally exposed to organic solvents and the other was not. With this study design the investigators were able to show inferior performance on several tests by the solvent-exposed twins.

Clinical Studies. As mentioned above, the self-selection of subjects for inclusion, which is inherent in studies of groups of patients, severely limits the possible conclusions based upon clinical studies. In spite of this fact, many such studies have been reported, especially from the Scandinavian countries.

Quantification of Exposure

Since the aim of behavioral toxicology is to establish a link between environmental exposure and a behavioral indication of a decreased functional capacity, it is evident that the quantification of exposure is essential to the success of our efforts. In spite of this, numerous studies have been (and still are) performed without paying sufficient attention to the measurement of the presumed cause of the effects observed. This is very clearly an area where much more effort should be spent in many behavioral studies.

Experimental Studies. Laboratory experiments are useful when the purpose of the study is to establish causal relationships or to investigate dose–effect relationships. To the extent that the investigator has full control over his independent variables, i.e., the exposure and extraneous factors, the risk for confounding of results can be minimized.

Nevertheless, a possible problem with laboratory studies is lack of representatvity of the exposures studied. Most experiments have been performed to investigate effects from exposure to a few stable concentrations of a single compound (37,38). Still, in the work environment, exposure to a single solvent is the exception, and stable exposure levels are likewise seldom found in industry.

When effects from more than a single compound are to be tested, the number of treatments, and the number of sessions needed in an appropriate experimental design, increases drastically. This is an important reason for the relatively modest number of studies that simultaneously test effects from exposure to more than one single solvent.

In our laboratory, the effects of compounds such as toluene in combination with xylene (39) and toluene in combination with ethanol intake (40) have been studied. In both of these investigations, a repeated-measurement design with four experimental conditions was employed. Other investigators have used designs with independent groups to study the effects of MIBK, MEK, and ethanol using six conditions (41,42), and of toluene, MEK, and ethanol using eight conditions (43). The design employing independent groups is, however, not the best one because the purpose of these studies was to compare the relative effects from the various treatments. Still, it is quite easy to imagine the many logistical problems (not to mention the difficulties in motivating the subjects) that would be involved when using a repeated-measurement design and eight experimental treatments.

Field Studies. In the quasi-experimental field study, effects from acute exposure are investigated. This is the reason for calling this study type experimental; the prefix "quasi" is added since the investigator has no actual control over the exposure. However, exposure is quite easily quantified in most cases since effect measurements are made directly at the work site.

Numerous field studies have been performed, studying, e.g., the effects from

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acute styrene exposure (25,44,45). Styrene is a solvent for which there are good biological indicators of exposure. This means that the exposure level or even the dose is fairly well described by analyzing biological samples such as urine or blood. Therefore, styrene was one of the first solvents for which good dose–response relationships were established. This was true in relation to acute effects of exposure as investigated in quasi-experimental field studies, as well as in cross-sectional studies of effects from long-lasting exposure.

Cross-sectional Studies. Although exposures in cross-sectional studies are generally quantified only using very crude estimates of the dose like painter years or merely a classification into categories like high/low, in some cases rather good measures have been obtained. For styrene, such measures may be obtained from biological indicators; for example, Hannu Härkönen et al. (16) were able to establish dose–response relationships for styrene. Later on, similar results were obtained by other research groups such as Cherry and her colleagues (46) and Mutti and his group (47).

In some rare instances, there have been series of relatively good measurements of solvent concentrations in ambient air. This was the case for Bleecker and colleagues (48–50), who studied the effects from long-term occupational solvent exposure in the paint industry. Such documentation of past exposure, however, is very rarely found, and the quantification of exposure is commonly the weakest part of studies in behavioral toxicology.

Clinical Studies. In clinical studies, exposure is likewise often very poorly defined. The most frequent classification is by occupation, or possibly by number of years employed in various occupations, but more detailed information regarding actual exposure levels or the composition of solvent mixtures is generally not available.

Test Methods

Another crucial aspect of the research methodology is obviously the test methods employed to quantify the behavioral effects. In the choice of test methods there are some noteworthy conflicts of interest. On one hand, it seems quite obvious to choose well-validated clinical tests to measure the impact from solvents on the nervous system since this choice implies some face validity and most probably a broader acceptance of the possible effects indicated. On the other hand, you would like to choose the most sensitive tests available to get early indications of possible effects, thus being able to work in a truly preventive manner.

Initially, clinical tests were applied in solvent research; with the very high exposure levels encountered in the 1960s and 1970s, effects were actually observed even when using these relatively insensitive methods. Still, a search was started in our laboratory to find tests that would be more sensitive to the early prenarctic effects from acute solvent exposure. Thus, as part of the early experimental work by Gambarle et al. (8–14), a series of tests and testing equipment were designed, thereby increasing the sensitivity of the studies.

The long tradition of test development in our laboratory includes not only the building of electronic equipment and the design of vigilance tests for experimental use but also a thorough standardization of a traditional clinical test battery using paper-and-pencil tests (51), which was reported internationally by Hogstedt and colleagues (52). A similar development took place in Helsinki, Finland, at the Institute of Occupational Health, where Hänninen and Lindström (53) developed and standardized their clinical battery, which has been applied in numerous studies during more than two decades.

A more recent trend in behavioral toxicology has been the development of computer-based tests and test batteries. Our laboratory has been engaged in this development for more than 15 years, and an extensive set of tests and rating scales, the SPEs, is now available for international use (54). Similar sets of tests have been developed by others: one well-known system pertaining to behavioral toxicology is the NES, developed by Letz and Baker (55). A review of computer-based test systems for use in neurobehavioral toxicology was recently presented by Iregren and Letz (56).

One problem encountered with modern, more sensitive test methods is the determination of which results of recent studies are adverse effects. Naturally, in studies of the impact of workplace exposure, it is debatable which effects should be considered normal. For example, most people would expect a certain amount of tiredness to be experienced at the end of a workday. On the other hand, feeling exhausted every day after work would not be accepted as normal by the majority of workers in the industrialized countries. Thus, some definition of adverse effect is desirable in behavioral toxicology.

Unfortunately, science and technology cannot help provide a solution because the definition of the concept of health is clearly not a scientific issue. Health must be defined on ethical grounds; once health is defined, scientific methods may be applied to study the possible impact on health from various exposures. Personally, I am convinced that however we decide to define the concept of health, behavioral methods will have helped and will continue to help us study the possible negative influence from, e.g., organic-solvent exposure.

Conclusions

The Scandinavian countries have been especially successful in the study of neurotoxic effects from exposure to organic solvents. A number of factors have contributed to this end, and I will briefly discuss four of these.

Social and Political Climate

The Scandinavian tradition, and especially the relationship between workers and employers and their respective organizations in Sweden, has been one of collaboration on matters of common concern since the 1930s. Furthermore, due to Swedish legislation on compensation for occupational illness, there has been no economic reason for companies to stop this kind of research. Thus, generally there has been no problem getting access to companies, workers, or data on the contamination of the work environment.

Multidisciplinary Approaches

While the discipline of behavioral toxicology basically uses behavioral outcome measures, we still need to know what causes the outcome that we measure. Therefore, behavioral scientists must collaborate with experts from a number of disciplines such as occupational hygiene and medicine as well as chemistry and physiology. For this reason, the Scandinavian type of multidisciplinary research institute is an ideal organization to set up the kind of research program needed for the successful study of effects from solvent exposures.

Research Strategies

In Scandinavia several groups of researchers have followed general, well-planned strategies for research. Thus, at the Swedish NIOH, the work on solvents began in an experimental laboratory setting; later on, effects from acute as well as long-term exposure in the workplace were studied, thus adding further experiences to the research group and still more impact from the results obtained on the regulatory authorities.
Methodological Development
Several research groups in Scandinavia have spent much time and effort developing tests and test batteries specifically for the early detection of effects from organic-solvent exposure. These extensive efforts at methodological development have certainly contributed to the consolidation of the research teams as well as to the results obtained.

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