

Human behavioral toxicology

Central nervous effects of low-dose exposure to neurotoxic substances in the work environment

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IREGREN A, GAMBERALE F. Human behavioral toxicology: central nervous effects of low-dose exposure to neurotoxic substances in the work environment. *Scand J Work Environ Health* 1990;16(suppl 1):17-25. The central nervous effects of low-dose exposure to the neurotoxic substances found in the work environment can manifest themselves both as adverse subjective reactions and as performance impairments and physiological changes. The acute manifestations of these effects can be studied under highly controlled conditions in laboratory experiments on volunteers or in quasi-experimental field studies on occupationally exposed workers. The effects of long-term occupational exposure are commonly studied with the use of epidemiologic techniques in cross-sectional investigations or cohort studies. In addition studies using data from clinical cases have been conducted to describe the chronic effects of exposure. Although these types of investigations can provide valuable information on the health hazards due to the neurotoxicity of different substances, their accomplishment encounters theoretical and practical problems, some of which are described and discussed in the present paper.

Key terms: behavioral effects, neurotoxic substances, occupational exposure, research methodology.

Classical toxicologic criteria based on obvious injury assessed with clinical, epidemiologic, or experimental methods have too often been found inadequate, in view of the continuously increasing demands for the prevention of health hazards to man from environmental exposure to chemicals. Indeed, the classical toxicologic approach based solely on lethality and/or advanced pathology implies an arbitrary safety factor. In the occupational environment today, exposure to chemical agents most commonly occurs at relatively low doses, which only rarely cause specific and definite pathological symptoms. However, the results of a large number of recent investigations clearly show that low-level exposure to several of the substances commonly found in the environment may cause impairment to the functional capacity of the nervous system. For this reason, toxicologists are currently taking an increasing interest in behavioral tests and procedures suitable for a quantitative evaluation of the effects of exposure to chemical substances also at low-dose levels. The major objective of this trend in modern toxicology is to find ways to detect, as early as possible, changes of systemic or nuisance nature that may be affecting humans.

Thus the ever increasing interest in behavioral toxicology is probably due to the sensitivity shown by psychological measurement techniques to unveil changes which otherwise would not be detected in the human organism. The evidence that these changes are among the earliest indicators of the occurrence of health

effects has, by now, become unequivocal. As a consequence the measurement of behavioral effects has come to be widely regarded as a device of major importance for the monitoring of potential health hazards. This development seems to agree with the definition of health put forward by the World Health Organization which has stated that health does not mean only absence of disease but also optimum physical, mental, and social well being and, moreover, that health not only means freedom from pain and disease, but also freedom to maintain and develop one's functional capabilities.

The neurotoxic work environment

Behavioral methods have been widely and successfully applied in many countries in studies of the neurotoxic effects from numerous compounds, such as organic solvents, anesthetic gases, heavy metals, and chemicals used in agriculture.

The following listing of potentially neurotoxic substances that are used in the work environment and have been investigated using behavioral methods is by no means exhaustive. The list summarizes the studies performed at our institute, and for each substance studied elsewhere only a single reference is given as an example. This list should, however, give the reader an idea of the potential of the use of behavioral methods within toxicologic research.

A large number of single solvents have been studied experimentally. At our laboratory methylene chloride (1), methyl isobutyl ketone (MIBK) (2), styrene (3), toluene (4) (5), 1,1,1-trichloroethane (6), trichloroethy-

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lene (7), white spirit (8), and xylene (9) have been studied. Still other solvents have been investigated elsewhere, eg, acetone (10), ethanol (11), formaldehyde (12), methyl chloride (13), methyl ethyl ketone (MEK) (14), and tetrachloroethylene (15).

Furthermore, the effects of a number of combinations of solvents have been investigated. At our institute we have studied toluene in combination with xylene (16) and in combination with ethanol (17). Other laboratories have investigated the effects of, eg, acetone and MEK (18), tetrachloroethylene and ethanol (15), toluene and MEK (14), trichloroethylene and ethanol (19), xylene and ethanol (20), and xylene and trichloroethane (21). Toxic gases that have been investigated experimentally include carbon monoxide (22), nitrous oxide (23), and halothane (24). The effects found in the studies of acute solvent exposures are generally slight, transient, narcotic effects, measured, eg, as prolonged response latencies in various tests.

At our laboratory, some cross-sectional investigations have been performed to study the potential toxic effects of long-term occupational exposures. These investigations included workers exposed to toluene (25), jet fuel (26), and mixed solvents (27). Other researchers have studied, eg, workers exposed to carbon disulfide (28), methylene chloride (29), and styrene (30) and also performed a number of investigations on groups of workers exposed to mixtures of solvents. The most commonly studied groups with mixed solvent exposure are house painters (31) and spray painters (32). The effects from long-term exposure to organic solvents seem to be very nonspecific and range from complaints of diffuse symptoms like fatigue or memory impairment to substantial reduction in intellectual functions, measured, eg, as concentration difficulties, memory problems, and decreased learning capacity.

We have recently investigated workers exposed to manganese (33), and other research groups have studied the effects of exposure to metals like lead (34) and mercury (35). There are also some studies on workers exposed to chemicals used in agriculture, eg, that of Metcalf & Holmes (36). The effects of long-term exposure to metals, eg, peripheral nervous system effects of mercury, appear to be more specific than the diffuse effects related to long-term solvent exposure. An increased tremor is often registered, and in severe cases the tremor may even be revealed in tests of eye-hand coordination.

As can be seen from these examples, behavioral methods have been applied in studies of effects of both short- and long-term exposure to a large number of potentially neurotoxic substances. Experimental studies on the acute manifestations of organic solvent toxicity have, for several compounds, provided information that has been used to determine industrial exposure standards. There is still, however, a controversy concerning the validity of the results of studies on the effects of long-term exposures. This is certainly the case regarding the possible effects of long-term occupa-

tional exposure to organic solvents. These discussions are beyond the scope of the present paper, and, for more comprehensive reviews of the research on effects from organic solvent exposure, see the reports by Dick (37), Gamberale (38), Grasso et al (39), Iregren (40), or Spencer & Schaumburg (41) as recommended.

Research problems

Route of exposure

To our knowledge no human experiment with the objective of studying behavioral effects has adopted dermal contact as a means of exposing subjects to solvents. Ingestion, which is the usual route of exposure in behavioral pharmacology, has also been the common procedure for administering doses in studies of the effects of alcohol. Experimental exposure to solvents has almost exclusively been brought about by inhalation of the solvent vapor. In long-term exposures the route may be, eg, inhalation (solvent vapors, exhaust fumes, or dust containing heavy metals) or ingestion (foodstuffs contaminated with metals, chemicals from agriculture, or other toxicants).

Exposure set-up

Exposure to gases or solvents can take place in an exposure chamber in which the gas or vapors are injected into the air of the chamber or, in special cases, by having the subjects inhale the agent through a mask or a breathing tube. The use of an exposure chamber enables several subjects to be exposed simultaneously. Moreover, the subjects can be exposed for much longer periods than is possible with a mask or other devices. For certain purposes, however, it might be of importance to expose subjects for very short periods of time, as is required in most psychophysical studies, or to avoid uptake of the agent through the skin. When effects of long-term exposures are studied, the possibilities for dermal uptake or uptake by ingestion of the toxic agent must also be taken into consideration.

Level of exposure

Experimental investigations may be directed towards the same behavioral effect or different behavioral effects at different levels of exposure. Thus, for some agents, psychophysical studies have been performed to assess the lowest level of exposure detectable by humans, ie, the perceptual threshold for the specific agent. Information concerning the perceptual thresholds is of particular importance for substances with irritating characteristics, eg, formaldehyde, carbon disulfide, and styrene. In most experiments, however, the aim has been to evaluate the risks for acute manifestations of toxicity in the central nervous system (CNS) in occupational exposure. For this reason, the specific objective has often been to assess the lowest level of exposure capable of causing functional impair-

ments to the nervous system. For ethical reasons, subjects are seldom exposed experimentally to concentrations above current exposure standards. Therefore experimental studies nowadays are often performed to evaluate occupational exposure limits or other standards. For new agents or mixtures of agents human experimental studies might contribute to the establishment of new exposure standards.

In studying the effects of past exposure conditions, the most difficult task is to obtain reliable exposure data. In most cases there is no way of estimating what the exposure has been at the individual level, and the investigator is often left only with information regarding average exposure at the group level. In some cases the investigator has to rely merely on information concerning the number of years the subjects have been employed in the exposed occupation.

Duration of exposure

According to the literature, humans have been experimentally exposed to, eg, solvent vapors for periods of time ranging from a few seconds to 8 h. Exposure periods of a few seconds have exclusively occurred in psychophysical studies aimed at the assessment of perceptual thresholds (12). Eight hours has been the length of exposure in some studies performed to investigate the adequacy of current occupational standards. More-detailed information on the duration of experimental exposure to solvent vapors in human experiments can be found in reviews by Gamberale (38) and Anshelm Olson (42).

It might be questioned whether it is necessary to expose subjects for 7 or 8 h in order to evaluate experimentally the adequacy of occupational exposure limits in eliminating risks for acute effects on central nervous functions. Even if occupational exposure limits and other exposure standards are intended for 8-h time-weighted averages, workers are very seldom exposed for this period of time without a lunch break or other pauses.

Variation of exposure over time

Some researchers have investigated and compared experimental exposure conditions which yield identical time-weighted averages but differ considerably with regard to the variation in exposure over time. In an experiment by Savolainen et al (43), eg, one experimental condition consisted of exposing subjects to a constant level of xylene, while in another condition the same time-weighted average was obtained for the concentration of xylene with considerable variation in exposure over time. Both these conditions of exposure occur frequently in the work environment. Thus, in a quasi-experimental field study of the acute effects of exposure to styrene in four shipyards (44), two groups of exposed workers, assemblers and resin appliers, were studied separately and were compared to

each other and to a group of unexposed workers. The two experiment groups were exposed to the same time-weighted average of styrene. However, while the assemblers were exposed to relatively low concentrations during the whole workday, the resin appliers were repeatedly exposed for short periods of time to relatively high concentrations of the solvent. Neither the experiment nor the field study gave sufficient evidence to allow conclusions about differences between the two conditions with regard to potential risks for acute effects.

The implications of variations in exposure levels for the development of effects from long-term exposures are not known. It has been suggested, however, that occasional high levels of exposure may be of particular importance in the development of chronic effects (45).

Control of exposure

The control of exposure in experimental studies is usually carried out through the monitoring of the concentration of the solvent vapor in inspired air. This control may be supplemented by biological measurements of the concentration of solvent in, eg, alveolar air, venous blood, arterial blood, or adipose tissues. Due to its effect on ventilation, physical work increases the uptake of the solvent in the body and influences its metabolism. Thus, in a few studies, exposure to solvents has been enhanced by the exposed subjects' working on a bicycle ergometer. In two of these studies (9, 43), it was shown that an increase in the uptake of a solvent, obtained with this method, could indeed be followed by an impairment in performance. In other studies (46) impairments in performance were related both to the concentration of the solvent in the inspired air and to the uptake of the solvent in the body as estimated on the basis of measurements of alveolar air concentration.

Regarding long-term exposures, there are seldom data on ambient exposure levels for individual workers. For some agents, however, data from biological monitoring may be available, such as blood levels of lead or styrene metabolites in urine.

Biotransformation

Many toxic compounds have to be transformed before they can be excreted, although some of the agent taken up may leave the organism unchanged in expired air, urine, or feces. The chemical processes involved in the biotransformation of many compounds, such as organic solvents, are not known in detail, although for some agents the enzyme systems involved in these processes have been explored. While the metabolic processes generally result in less toxic intermediates, for some agents reactive metabolites are produced which are more toxic than the original compound.

Effect mechanisms

Although very little is known about the actual physiological processes underlying normal central nervous functions, there is a rapidly growing body of knowledge concerning the specific neurochemical effects of exposure to various agents. For most neurotoxic compounds the exact mechanism of action is still not fully understood, but several possible ways of causing toxic effects in the CNS are known. A disturbance of neuronal functioning due to exposure to neurotoxic substances could be caused by effects on, eg, cell membranes, axonal transportation, and cell metabolism or by interference with synaptic functions through changes in neurotransmitter balance.

Type of effects

Various types of interactions, eg, additive, synergistic, or antagonistic, may occur in exposure to mixtures of chemicals. The effects from a mixture may be equal to, worse than, and in some cases even less than the mere sum of the separate effects. Additive effects are generally assumed when exposure norms are established. It has been shown, however, that the effects from some combinations of agents, which are relatively harmless separately, may potentiate each other strongly.

Individual susceptibility

The large interindividual variation in responses to irritating compounds is a well known fact. For many irritating agents, it has been established that individuals with a predisposition for allergic reactions exhibit much stronger reactions than others. Similar differences between individuals have been proposed to account for the large variation observed in CNS responses to long-term exposures. However, to our knowledge, no studies pertaining to this question have been reported so far.

Reversibility of effects

The degree of reversibility of effects from environmental toxicants is dependent on, eg, the toxicity of the specific agent, the level of exposure, the length of the exposure period, and the susceptibility of the individual affected. Although very little is known about

the actual mechanisms by which various toxicants exert their influence on the organism, it is believed that the effects may be reversible as long as there is no structural damage to the nervous system.

Three effect continua

The neurotoxic effects caused by exposure to unfavorable environmental conditions are generally assessed with analyses of the changes in individual response which may occur as a result of impairments in the functional capacity of the nervous system. These impairments might be indicated by measurements in any or all of the three effect domains illustrated in figure 1.

Perception

The perceptual domain includes all kinds of subjective reactions, eg, sensations, feelings, symptoms. These reactions are usually assessed with the use of interviews, questionnaires, and rating scales or by classical psychophysical methods.

Performance

The performance domain includes all kinds of objective measures of the capacity of the nervous system with regard to sensory, perceptual, cognitive, and motor functions. Over the years, many tests and batteries have been applied in behavioral toxicology, and a recent trend has been the computerization of tests. Reasons for this trend can be found in the many potential benefits from automated or computerized testing, which include an opportunity for strict standardization of test procedures, possibilities to perform detailed measurement and analysis of single responses or response components, and an increased precision in the measurement procedure. The computerized systems are flexible and thus can be used to administer a variety of tests and to facilitate prompt scoring and evaluation of the results. Furthermore, computers are transportable and thus make field testing feasible.

Some possible implications of computerized testing have been criticized. Two critical points made are the supposedly poor rapport between the subject and the machine and the static form of computerized testing. Furthermore, computerized testing implies difficulties

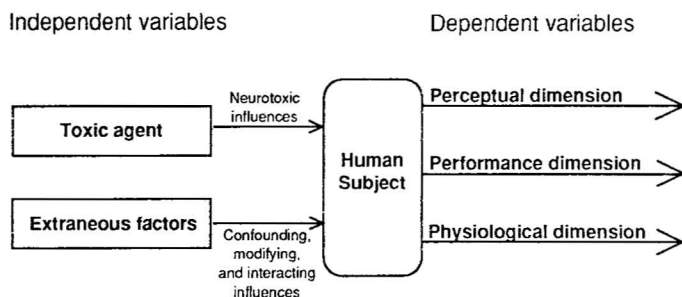


Figure 1. Model of the three effect domains in behavioral toxicology research. The toxic effects of exposure and the confounding effects of extraneous factors (independent variables) are observed as changes in the perceptual, performance, and physiological variables (dependent variables).

in testing large groups, and, most important, it implies restrictions with respect to both stimulus and response modes.

Since administration of, eg, auditory or tactile stimuli require the use of rather complicated external equipment, the implementations of performance tests on computers have almost exclusively relied upon visual stimuli. The few response media available present a similar problem with respect to the development of tests. Since input to a computer is normally made via the keyboard, most testing systems are currently restricted to this medium. Attempts to use other means of input usually also imply manual performance, as, eg, with joy-sticks or touch sensitive screens. These restrictions are, at present, limiting factors in the development of standardized computerized test batteries. Access to a fast and reliable system for processing speech input would, of course, provide a much better solution.

In spite of the limitations, the use of computerized testing systems is steadily increasing. One example is the system currently in use at our laboratory, the Swedish Performance Evaluation System (SPES) (47). This system has evolved over many years to meet our needs in toxicologic research, and it is thus well established. In addition to several performance tests, it contains several rating scales for the measurement of mood, symptoms, and subjective effort.

Various aspects of computerized testing have been treated in recent reviews by, eg, Bartram & Bayliss (48), McArthur & Choppin (49), Space (50), and Thompson & Wilson (51).

Physiology

The physiological domain covers all measures, especially electrophysiological ones, which might reveal functional changes in the central or peripheral nervous system. Of special interest in this context are the measures collected by electroencephalographic methods and the measures of peripheral nerve conduction in major sensory and motor pathways.

Study design

Various research strategies and types of studies are represented within human behavioral toxicology research. To give a general idea of the variety of investigations performed in this field of research, a few study types will be described and discussed briefly. They are (i) an experimental laboratory study, (ii) a quasi-experimental field study, (iii) a cross-sectional epidemiologic investigation, (iv) an epidemiologic register study, and (v) a study based on clinical observations.

Experimental laboratory studies

An investigation of the acute effects of exposure to toluene in combination with ethanol intake reported by Iregren et al (17) will serve as an example of an experimental laboratory study.

The objective of this experiment was to study whether exposure to toluene at a level corresponding to the Swedish exposure standard (80 ppm or 300 mg/m³) for 4.5 h and ingestion of ethanol (15 mmol/kg) could induce behavioral effects. This goal was accomplished by studying the results of four computerized psychometric tests, by registering symptoms and mood changes, and by recording physiological indices of wakefulness for 12 male volunteers under four different experimental conditions. The experimental conditions which were compared included (i) exposure to toluene, (ii) intake of ethanol, (iii) exposure to toluene and intake of ethanol, and (iv) control conditions. Toluene exposure produced symptoms like headache and local irritation, and a weak depression of heart rate during rest as well, but it did not reduce performance capability. Ethanol ingestion impaired performance on two of the tests and also increased heart rate. Mood was likewise altered by ethanol, but no increase in subjective symptoms due to ethanol ingestion could be demonstrated. Physiological indices of wakefulness were not affected either by toluene exposure or by ethanol intake. No interaction effects were found.

Within behavioral toxicology, experimental studies of the type described have been conducted primarily to study the risks for acute effects on the nervous system when workers are exposed to the low concentrations of neurotoxic substances commonly encountered in the work environment. Since the experimental procedure allows the manipulation of exposure and the control of known confounding influences, laboratory experiments are especially suitable for establishing dose-response relationships, which is one of the primary goals in toxicology.

The most evident limitation of the experiment as a research strategy is that it cannot directly generate data of interest for the evaluation of effects from long-term exposure. In spite of this limit, experiments have often been performed to establish entirely new exposure standards or to evaluate already existing standards.

Experiments are often criticized for their lack of representativeness with respect to the exposure situation and with respect to the selection of subjects. In fact, in most respects the exposure situation in the real work environment cannot be simulated in an exposure chamber. The extent to which results obtained in the exposure chamber can be generalized to the exposure situation encountered in the work environment is open to debate. In addition, for practical and safety reasons, the subjects participating in inhalation studies are often chosen from "healthy young male students." There are, however, a few studies (eg, references 5 and 52) in which occupationally exposed workers of varying ages have been experimentally exposed. In these cases

the results have not been different from those obtained with young, healthy volunteers.

The aforementioned limitations of the experiment as a research strategy in behavioral toxicology are part of the rationale for performing so-called quasi-experimental field studies.

Quasi-experimental field studies

A field study that was reported by Anshelm Olson (53) on workers in the paint industry will serve as an example of this type of study design.

The study was conducted to investigate the effects on the CNS function of paint industry workers who were exposed daily to a mixture of organic solvents. Forty-seven solvent-exposed workers and forty-seven age-matched unexposed industrial workers were examined before and after a workday with a battery of tests including reaction time, perceptual speed, short-term memory, and critical flicker fusion. A questionnaire was used to assess subjective symptoms. The exposed group consisted of workers who had been occupationally exposed for more than 10 years or were exposed to concentrations of solvents clearly above the occupational exposure limits at the time of the investigation. On the average, the exposed workers performed less well than the unexposed group on the tests. The differences were the most pronounced in the measurements performed after the workday for the group exposed to higher solvent concentrations. The result could be interpreted as primarily due to an acute effect of exposure to the solvent mixtures.

This investigation, which can be regarded as a quasi-experiment, gives an interesting illustration of how behavioral changes during the workshift may be associated with acute effects of solvent exposure.

The characteristic feature of this type of study is that measurements of the dependent variables are performed both at the beginning and at the end of a workday. The rationale of this design is based on the underlying assumption that the effect of solvent exposure during the day may manifest itself at the end of a workday with a return to normality by the beginning of the following workday, after approximately 16 h free from exposure. If, on the contrary, the action of the exposure to solvent vapors lasts long enough to bridge the exposure-free period between two consecutive workdays, the behavioral variables should be negatively affected also at the start of a workday.

The application of this study design does, however, require very careful planning and thorough experimental control, since the results may easily be biased by various confounding factors associated with the selection of workers. Furthermore, when measures of behavioral variables have to be carried out at different times during the day, circadian rhythms, learning, and motivation may constitute confounding factors. It is, eg, necessary, as an operation of experimental control, that half of the workers in the exposed and in the age-

matched control group be examined before work the first time and after work the second time, whereas the other half must be examined after work the first time and before work the second time.

Cross-sectional epidemiologic studies

A study of the performance effects of low-dose exposure to manganese in Swedish foundry workers, recently presented by Iregren (33), will exemplify the cross-sectional study. A group of 30 manganese-exposed workers from two worksites and a reference group of 60 workers matched for age, geographic area, and type of work were studied with a comprehensive computerized test battery. Manganese exposure was found to be relatively low, varying between approximately 1 and 50 % of the Swedish exposure limit of 2.5 mg/m³, and the duration of exposure was from 1 to 35 years. In the evaluation of the results a difference was found between the groups in a test of verbal ability. As this difference was believed to indicate a premorbid difference in general cognitive abilities, a secondary matching of the groups was performed. It added verbal test scores to the matching criteria. Following this secondary matching the performance of the exposed group was still inferior to that of the reference group on tests of simple reaction time, memory span, and finger tapping. These results were interpreted by the author as indicating a risk for adverse effects on the CNS at levels of exposure clearly below the Swedish standards for this substance.

There are, however, a number of difficulties in the interpretation of group differences in behavioral measures found in cross-sectional studies. When comparing the results from two groups, one makes the assumption that the groups were actually comparable with respect to the outcome variable prior to exposure. There is unfortunately no way to ascertain this assumed comparability when psychological effects are being dealt with. Matching has often been tried, but the number of potentially confounding variables is so great that matching for all of them is practically impossible.

In clinical neuropsychology, it is common practice to regard the results on tests of verbal ability as being relatively resistant to diffuse organic CNS damage. This hypothesis about "hold-tests" has been introduced in behavioral toxicology, where the results on more intellectual tests have been assumed to indicate premorbid cognitive abilities. Thus secondary matching or statistical corrections for verbal ability have often been applied, eg, by Hänninen et al (32) in their study of car painters and by Hane et al (54) and Lindström & Wickström (31) in studies of house painters. Hänninen et al (32) compared car painters to a group of railway engineers and found the exposed group inferior on cognitive tests. This difference was eliminated by a secondary matching. In the study by Hane et al (54) house painters were compared to a mixed group of industrial workers, who performed

worse than the painters on a verbal test. In this study the verbal test score was used for statistical manipulations aimed at making the groups comparable. Lindström & Wickström (31) compared house painters to concrete reinforcement workers and found the reference group to have higher scores on intellectual tests. In this study results from preexposure intelligence tests, performed during the military service, were used for a secondary matching. The validity of any of these practices is uncertain, but the main point that should be made is that the groups *de facto* were not comparable in the first place. Any effort at secondary corrections of this incomparability is certainly debatable.

Epidemiologic register studies

Data from various registers have been utilized in epidemiologic studies to obtain information regarding the possible neuropsychiatric effects of long-term exposures to neurotoxic substances. These research strategies should thus be mentioned in this context, although they do not imply direct behavioral measurements. A few studies have been conducted to investigate the role of solvent exposure as a cause of disability pension due to neuropsychiatric disorders. Thus, in a case-referent study, Axelson and colleagues (55) found occupations with solvent exposure to be overrepresented among disabled workers. Similar results were obtained in a cohort study performed by Mikkelsen (56), who found an increased risk for disability pension due to presenile dementia in a cohort of Danish painters. Since an evaluation of the epidemiologic techniques is beyond the scope of the present paper, the interested reader is referred to, eg, Hernberg (57) for a further discussion of methodological problems in the use of these strategies and to the review by Grasso et al (39) for a discussion of the results.

Studies based on clinical data

Clinical data from three different applications (58, 59, and unpublished data) of the test of simple reaction time from the SPES battery will serve as an illustration of the clinical uses of behavioral toxicology.

In the three clinical applications of the reaction-time test a total of nearly 200 patients, referred to different clinics of occupational medicine with suspected solvent-induced occupational disease, were tested. Figure 2 shows the position of the mean reaction time for different diagnostic groups as compared with the distribution of reaction times in a population of 424 industrial workers without solvent exposure. From the figure it can easily be seen that the groups differed markedly in their performance on the test. However, the figure gives no information on the predictive value of the results of this test with respect to the diagnosis of solvent-induced illness on an individual basis.

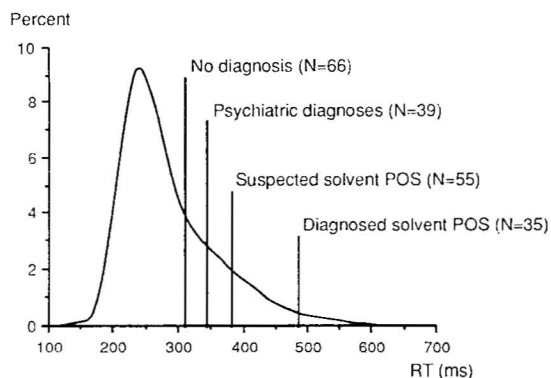


Figure 2. Position of the mean reaction time for different diagnostic groups as compared with the distribution of reaction times in a population of 424 industrial workers without solvent exposure. (POS = psychoorganic syndrome, RT = reaction time)

Concluding remarks

There seems to be various reasons for the use of behavioral methods in toxicologic studies. One is that behavioral methods have proved to be more sensitive in many instances than traditional neurological or neurophysiological methods in situations involving low-dose exposure. This characteristic of the behavioral methods makes them especially useful in generating adequate data for the evaluation of existing exposure standards for known neurotoxic substances, or for the establishment of new such standards for substances not previously known to be neurotoxic. Because of their sensitivity, behavioral methods may reveal early signs of functional disorders and thereby provide useful means for preventing later manifestations of irreversible damage. Finally, and most important, behavioral measures may contribute to a successful implementation of employee monitoring programs for neurotoxic substances. One example would be the systematic collection of behavioral data for follow-up health assessment and effect monitoring.

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