

Short Duration Exposures to Organic Solvents: The Relationship Between Neurobehavioral Test Results and Other Indicators

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DICK, R. B. *Short duration exposures to organic solvents: The relationship between neurobehavioral test results and other indicators.* NEUROTOXICOL TERATOL 10(1) 39-50, 1988.—Short duration exposure to solvents at even low concentrations can induce signs of mild toxicity such as mucous membrane irritation, tearing, nasal irritation, headache, and nausea. These irritant effects are often used as warning properties for potential solvent toxicities and have frequently been classified in the literature as pre-narcotic effects. With higher exposures the toxic effects are more pronounced and can include intoxication, incoordination, exhilaration, sleepiness, stupor, and the beginning stages of anesthesia. Collectively these effects are taken as indicators of narcosis. Offering recommendations for safe exposure limits for these shorter term exposures is made difficult because, (1) the mild toxic effects are often reported subjectively and tolerance usually develops, (2) the solvent concentration(s) cannot be documented in all cases, and (3) the effects are reversible when individuals are removed from exposure. Laboratory experiments involving controlled exposures to solvents using neurobehavioral performance tests represent one form of investigation that can provide meaningful information in this instance. The results can be viewed in two ways with reference to issues of safe exposure limits. One is to ensure that performance functions that can compromise safety are not affected by the exposure limits prescribed. The second is to consider performance changes due to short-term exposures as possible precursors of similar but more severe effects given longer term exposures. Thus, setting exposure limits to protect against these performance changes could possibly prevent the development of more serious cases of chronic solvent neurotoxicity. This paper compares solvent concentrations from short-duration exposure studies using neurobehavioral tests with the concentrations producing irritant and narcotic effects, as documented by the two main standards recommending bodies, the National Institute for Occupational Safety and Health and the American Conference of Governmental Industrial Hygienists. Comparisons are also made with the regulatory exposure limits established by the Occupational Safety and Health Administration. In general, the neurobehavioral changes which occur following short-duration exposures are reported at concentrations between those which produce irritant effects and narcosis. For the chemicals which have been tested, the performance changes measured by the present day neurobehavioral tests in use rarely occur at or below those limits recommended by the standards recommending bodies.

Human exposures	Neurobehavioral testing	Organic solvents	Irritant effects	Narcotic effects
Standards	Acute effects	Chronic effects	Risk assessment	

RECENT interest in the chronic effects of long term exposure to solvents [8] raises several important research questions. These range from the adequacy of present day workplace exposure limits to prevent the acute effects of solvent exposures to definitive research strategies for predicting the potential of chronic effects from repeated exposures. This paper seeks to address these issues and suggest the advantages of incorporating a wider array of behavioral indices in the decision making process for setting exposure limits.

The central nervous system (CNS) effects produced by exposure to solvents necessitates consideration of a new domain of test procedures to augment the traditional methods of toxicity testing. Neurobehavioral tests that measure basic psycho-physiological functions of alertness,

reaction time, memory and sensory-motor performance have the potential to be sensitive indicators of mild central nervous system effects. Recent reviews [4, 8, 12, 23, 26] have outlined the problems, summarized the tests and chemicals used in both short duration and long term exposure studies, and have begun to present an operational framework for the assessment of neurotoxic effects through the use of neurobehavioral tests and research strategies. This paper will compare behavioral performance information documented in the literature from short duration exposures with other indicators of neurotoxicity which have been reported from similar short exposure durations. Additionally, this information will be examined for its usefulness in establishing recommendations for exposure limits to prevent acute ef-

fects and, possibly, chronic effects from longer term solvent exposures. Preventing exposures that produce acute effects will reduce the potential for development of chronic effects, because total cumulative exposure concentrations are lower. However, even with reduced exposure levels, the development of chronic solvent neurotoxicities cannot be entirely eliminated.

Apart from the acute effects of solvents, solvent neurotoxicity does not at present have a universally accepted definition. This is due in part to the complexity of the nervous system. Through the sponsorship of the World Health Organization (WHO), some working definitions have been proposed dividing solvent neurotoxicity into two general classes with several sub-definitions [9]. The two general types are (A) Acute Organic Mental Disorders, and (B) Chronic Organic Mental Disorders. Acute Organic Mental Disorders result from short duration exposures at higher concentrations and are further subdivided into acute intoxication and acute toxic encephalopathy. Chronic Organic Disorders are subdivided into organic affective syndrome, mild chronic toxic encephalopathy, and severe chronic toxic encephalopathy. In general, when the chronic conditions are present, several CNS functions, such as psychomotor functions (speed, attention, dexterity), memory, abstract thinking, judgement, and mood are severely impaired. Such conditions are sometimes reversible if individuals are removed from the exposure situations [9]. Chronic disorders (organic affective syndrome and mild chronic toxic encephalopathy) appear to represent more severe manifestations of the type of CNS depression and psychomotor impairment present during an episode of acute solvent intoxication.

Most of the similarities between the acute and chronic disorders occur in the realm of psychomotor impairment. Psychomotor impairment detected during short duration exposures occurs at concentrations lower than those reported to produce overt signs of narcosis or intoxication. Psychomotor impairments during low level exposures may be the precursors of more severe toxicities that could occur over prolonged exposures despite the absence of overt signs of narcosis and the rapid recovery from the intoxicating symptoms. This relationship has most recently been stated in a report from an international symposium on neurobehavioral methods in occupational and environmental health: "Neurobehavioral effects may well be perceived by the individual at a time when functional changes are not readily demonstrated, and significant morphological signs may occur only at a late stage," (p. 11, [65]). With the increased emphasis on, and more widespread acceptance of the chronic conditions (defined above) resulting from solvent exposures, it is also important to recognize the health implications of the body of research available from controlled short duration studies. Indeed, the nature of such information can enhance worker safety both by preventing the reversible adverse CNS effects, which may contribute to the potential for accidents, and by retarding the development of long term chronic effects. In other words, by preventing the regular occurrence of the acute reversible effects, the long term chronic disorders are less likely to develop [65].

RESEARCH STRATEGIES

While the emphasis in this paper will be on short duration exposure research, a brief discussion of the research approaches available for delineating the course of solvent neurotoxicity is appropriate. A more in-depth review of the research methods with behavioral performance tests has

been provided by Gamberale [23]. Ideally, research on human subjects is the most desirable, but definitive controlled laboratory studies of chronic exposures using humans as test subjects are ethically unacceptable because of the possibility of irreversible health effects. Paradigms acceptable for human research using neurobehavioral tests are usually limited to retrospective epidemiological studies, clinical case studies, worksite evaluations, and controlled laboratory short duration exposure studies. Epidemiological and clinical case studies usually cannot document chemical exposure concentrations accurately nor relate current body burden or exposure with the symptoms and clinical effects reported. In many cases, these studies represent the only choice because development of solvent neurotoxicity may take several years, and employees may have worked in several different types of jobs over the course of their work history. Worksite studies on factory-exposed workers can document exposure concentrations at the time of the study, but have difficulties when it comes to reconstructing past exposure levels. In some cases, studies report current exposure concentrations while testing a population which also has long term exposures. In addition, a worksite study requires a non-exposed referent group with a similar work history and the permission of a cooperative plant, which are sometimes significant or major obstacles. On the other hand, this type of study does provide a more realistic evaluation because it is done at an actual worksite, reflects actual workload conditions and can include opportunities to test for effects during different periods of exposure.

Laboratory research offers another approach. It allows for complete control over exposure conditions, selection of subjects and the test environment. The laboratory setting provides greater experimental precision to isolate chemical from non-chemical effects. Subjects may be exposed once or several times to one chemical, or combinations of chemicals, usually at low level concentrations, and neurobehavioral test measurements can be taken before, during and after exposure. In the typical experiment, exposures are usually constant and durations run 2-6 hours. Biochemical indicators of body burden levels (blood, breath, urinary metabolites) can also be studied for individual differences and correlated with performance levels. A few experiments have used fluctuating exposures [45] and/or physical exercise [28,32] to simulate work load conditions, which is probably more representative of the actual workplace situation. However, in these experiments, experimental control and statistical analysis can be more difficult, and it is also harder to pinpoint the actual concentration at which effects first appear in comparison to constant exposure studies with sedentary subjects. For example, physical exercise increases solvent uptake [6] especially to the CNS, which can lower the concentration-effect thresholds for certain tasks. Additionally, although not a major interest of this paper, studies have been conducted with ethanol in combination with solvent exposures to investigate the interactions of the two CNS depressants [41,62].

Ethically, human laboratory studies must provide adequate margins of safety and thus are limited to low level, short duration exposures with chemicals posing little risk. This may reduce the number of chemicals that can be studied, eliminating those for which inadequate information exists concerning their toxicity. The delineation of dose-effect information is also limited because most investigators are reluctant to test at levels where the overt intoxicating effects are present. Although it would be possible to expose subjects for periods of several weeks or more under con-

trolled conditions (to approximate some longer term exposure conditions), such studies are rare [51]. Most short duration studies expose the subjects only once to one concentration, or not more than a total of 6–10 times at one or multiple concentrations [41]. When subjects are exposed successively, there are often several days of separation between exposure periods unless the cumulative effects of solvent build up are the object of investigation [29].

Short Duration Laboratory Exposure Research

Presently, many of the exposure limits offered by the standards-recommending bodies (the National Institute for Occupational Safety and Health [NIOSH], and the American Conference of Governmental Industrial Hygienists [ACGIH]) do use data from short duration studies when it is available. These are often reported as irritant and/or narcotic effects, and maximum exposure concentrations are sometimes set to prevent the onset of both types of effects as they do represent a continuum depending on the concentration and duration of exposure. However, the use of short-term exposure research findings to predict effects from long term exposures is not apparent.

Irritant effects generally include mucous membrane irritation; odor, eye, nose and throat irritation, mild headache, nausea and slight incoordination. These are often referred to as the warning properties for solvent exposures and tolerance usually develops in most exposed individuals. With higher exposure levels or with prolonged durations, overt effects can be produced. These include the irritant effects noted above, plus sleepiness, drowsiness, exhilaration, excitability, motor instability, narcosis (stupor) and the beginning stages of anesthesia. These are often referred to collectively, as narcotic effects. The effects reported from solvent exposures advance along a continuum from irritant to overt narcotic effects, which produces some confusion in the reporting of narcotic effect levels. In this paper, narcotic effects will mean levels where definite signs of narcosis are present.

Frequently, subjective reporting has been used to document solvent exposure effects. This can lead to unreliable results, because for several solvents, the olfactory thresholds are so low it is sometimes difficult to separate true CNS effects from situational effects (*viz.*, subjects knew they were in an exposure situation). In addition, irritant effects are usually reported at concentrations lower than the other indicators of systemic toxicity (hepatotoxicity, kidney dysfunction, neurotoxicity) [46]. As mentioned previously, tolerance to the irritant effects can occur rapidly and there is often a sizeable concentration gap between the irritant effect levels and the levels where the other more verifiable narcotic effects indicators appear for some solvents. The use of more objective measures of toxicity such as neurobehavioral tests to identify effects at the lower concentrations, can fill this void. Neurobehavioral test results can be indicators of sub-clinical toxic effects which are often attributed to mild CNS depression.

It is quite possible to test for several functions relating to central nervous system processes. These include sensory and motor functions, cognitive processing, psychomotor abilities, memory, alertness, attention, and coordination. Tests and measurements of these functions used in neurobehavioral toxicology research can be either neuropsychological or physiological, or a combination of both. They include simple/choice reaction time, recognition/recall memory, auditory/visual evoked potentials, electronystag-

mography, electromyography, mental processing (e.g., number addition, learning), vigilance (auditory and visual), tracking, postural sway, balance acuity (visual and auditory), and manual dexterity. From examination of the literature the most sensitive tests for detecting solvent effects appear to be simple and choice reaction time, critical flicker fusion (CFF), vigilance, dual tasks, postural sway, vestibulo-oculomotor tasks, evoked potentials and manual dexterity. Tests which manipulate task parameters, and/or are automated also improve the sensitivity, by improving the measurement precision.

In summary, the use of neurobehavioral tests in laboratory settings would yield test results under conditions affording tighter control of exposure and situational variables. Results produced from such studies would be an improvement over the highly subjective irritant or narcotic effect information reported for many solvents cited by the standards/recommending bodies referenced in this paper.

Irritant, Narcotic and Neurobehavioral Effects vs. Established Limits

Examination of the literature on short duration solvent exposure studies allows some comparisons to be made between concentrations at which behavioral test measurements indicate statistically significant changes and the reported exposure levels at which irritant and narcotic effects occur. A second comparison can contrast these concentration values with the maximum concentrations promulgated or recommended by regulatory (US Dept. of Labor, Occupational Safety and Health Administration-OSHA) and research agencies (NIOSH) and a professional standards-recommending groups (ACGIH). In addition, many studies are testing at the present day recommended exposure concentrations, with confirmatory body burden indicators, which can provide another comparison. Shortcomings exist with these comparisons, including the limited number of chemicals studied and the general applicability of the findings to the actual workplace setting.

Neurobehavioral performance test results in short duration studies do not show marked neurotoxic effects at present day recommended limits for most solvents, but some effects are noted at concentrations which fall between those yielding irritant and narcotic effects. In Table 1 are listed, left to right, the chemicals that have been tested in controlled laboratory studies; the recommended workday and ceiling or short term exposure limits (STELs) as prescribed by NIOSH [59,60], ACGIH [1,2], and OSHA [61]; reported concentrations which produce irritant effects; concentrations reported to produce neurobehavioral test effects, exposure durations, the effects which have been reported using behavioral performance tests and the number of subjects tested. The last column reports concentrations where overt indications of narcosis should be present. In this column are the immediately dangerous to life or health levels (IDLH) [60]. The IDLH level represents a maximum level from which one could escape within 30 minutes without any irreversible health effects. Because several of the IDLH concentrations are equal to or greater than concentrations reported in the literature documenting narcotic effects, they should be considered at the upper end of true narcotic effect levels. Although the IDLH levels have not been updated since 1971 and are designed primarily for respiratory protection, they do offer for comparison purposes an operationally defined health effects level. The OSHA Permissible Exposure Limits

TABLE 1
COMPARISON OF INDICES (ppm) OF CNS EFFECTS AT LEVELS REPORTED (ppm) FOR NEUROBEHAVIORAL EFFECTS WITH THE EXPOSURE STANDARDS (ppm)

Chemical			Neurobehavioral				Narcosis IDLH
NIOSH REL (a)	ACGIH TLV (b)	OSHA PEL (c)	Irritant Effects	(Concentration	Duration ^d	Effects Subjects)	
Methyl chloride							
LFL ^e	50 100	100 200	—	200	3 hr	Slight impairment (4%)—visual time discrimination; dual task 56S [36]	10,000
				150	1–7.5 hr	Time discrimination-slight impairment 4S [52]	
Methylene chloride							
LFL ^e	50 ^f	500	—	>300	3 hr	Auditory Vigilance and CFF 12S [63]	5000
500	175 ^f	1000		200	4 hr	Dual task, Auditory vigilance after 3 hr 12S [35]	
Styrene							
50	50	100	100 [1]	>375	2–7 hr	Romberg test, dexterity, coordination 9S [47]	5000
100	100	200	200 [61]	>350	30 min	Simple RT (5% decrement) 12 S [18]	
				>50	1 hr	Reaction time (RT) and attention 5S ^g [34]	
				87–139 ^h	1 hr	Vestibulo-oculomotor tests 10S [32]	
Trichloroethylene							
25	50 200	100 200	50 [1] 200 [56]	>300	2.75 hr	Necker cube test 1S [54]	1000
				>500	2.75 hr	Manual Dexterity 1S [54]	
				>1000	2 hr	Depth perception, Purdue Peg., hand steadiness 8S [57]	
				>300 ⁱ	2 hr	CFF, depth and form perception hand steadiness 6S [15]	
				110	8 hr	Perception, memory, RT, manual dexterity 6S [39]	
				32–78 ^j	1 hr	Vestibulo-oculomotor tests 10S [28]	
1,1,1-Trichloroethane							
200	350	350	500 [61]	500	6–7 hr/5 days	Romberg test 5S [48]	1000
350	450	—	>1000 [56]	>350	30 min	Perceptual speed 12S [17]	
				>450	30 min	Dexterity, RT 12S [17]	
Tetrachloroethylene							
MWL ^k	50 200	100 200	>200 [61] >200 [1]	104	7 hr	Romberg test—17S [49] Moderate effects not replicated in later study [53]	500
Toluene							
100	100	200	100–200	>300	20 min	Simple RT 12S [16]	2000
200	150	500	[61] 200 [40]	>500	20 min	Choice RT 12S [16]	
				240	1 hr	Auditory Vigilance 11S [24]	
				126–157 ^l	1 hr	Vestibulo-oculomotor tests 15S [25]	

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TABLE 1
(Continued)

Chemical	ACGIH TLV (b)	OSHA PEL (c)	Irritant Effects	Neurobehavioral (Concentration Duration ^d Effects Subjects)			Narcosis IDLH
NIOSH REL (a)							
Xylene							
100	100	100	200 [56]	>300 ^m	70 min	RT for addition, choice RT, short term memory 15S [22]	1000
200	150	8 hr TWA	200 [1]	100-200 ⁿ	4 hr	Whole body sway, choice and simple RT 8S [41,43]	
				100-400 ^o	6 hr	Whole body sway, RT, CFF 6S [42]	
				126-400 ^o	4 hr	Whole body sway (eyes closed) 9S [45]	
Acetone							
250	750	1000	500 [1]	250	6 hr/6 days	Simple RT (5%) 6S [29]	20,000
	1000		200 [58]	500	6 hr/6 days	Simple RT (10%) 6S [29]	
FC-113^p							
	1000	1000	500 [1]	>2500	2.45 hr	Manual dexterity, vigilance, card sorting 2S [54]	4500
	1250		2500 [7] (est)				
White spirit^q							
60	100	500	150 [1]	760	50 min	Simple RT and short term memory 8S [20]	5000
310	1000		400 [61]				

^aNIOSH REL—1st value in column is time-weighted average (TWA)-10 hr day and value below it is ceiling value (15 min).
^bTLV—Documentation of Threshold Limit Values, 4th ed. 1st value is 8 hr TWA and 2nd is short term exposure level (STEL).
^cPEL—Permissible Exposure Limits. 1st value is 8 hr TWA and 2nd is ceiling.
^dDuration—min=minutes; hr=hours; days.
^eLFL—Lowest Feasible Level.
^fProposed change—1986-87 TLV[®].
^gThree of the five subjects had occupational exposure to styrene.
^hWith 50w physical exercise.
ⁱWith 50w physical exercise.
^jEthanol in combination with the chemical exposure.
^kMWL—Minimize Workplace levels
^lWith 50w physical exercise.
^mExercise at a set work load during the chemical exposure.
ⁿEthanol/Physical exercise in combination with the chemical exposure.
^oThe exposure level was fluctuating and not constant.
^pFluorocarbon-113 (1,1,2-Trichloro-1,1,1-trifluoroethane).
^qStoddard Solvent (Values are reported in mg/m³, but have been converted to estimated ppm values for this table).

(PELs) represent regulatory limits having the force of law; this sets them apart from the NIOSH Recommended Exposure Limits (REL's) and ACGIH Threshold Limit Values (TLVs[®]) which are recommendations. The concentrations producing irritant effects are principally drawn from secondary reference sources [1, 6, 7, 40, 56, 58, 61], while the neurobehavioral results were extracted from the primary sources. The references are listed in the Tables. No attempt has been made to indicate the quality of studies reporting effects. A recent review [12] does provide critiques to most of the studies used in this paper.

Table 1 shows that the exposure concentrations at which statistically significant neurobehavioral test decrements are reported can occur roughly between the concentrations that produce irritant and narcotic effects. Exposures are usually

constant using sedentary subjects (exceptions are noted), and durations in most studies average 4 hours, although some are as short as 30 min. However, exposure durations between the three indicators used in Table 1 are not always consistent. With four chemicals (1,1,1-trichloroethane, tetrachloroethylene, acetone and styrene), the concentrations reported to produce behavioral effects are at or below the reported irritant effect concentrations.

Table 2 provides a comparison indicating where concentrations have been tested near or below either the NIOSH REL's or the ACGIH TLVs[®] and where no behavioral performance changes, as measured by the tests used, have been reported. Some studies appear in both tables (1 and 2) because the listings are by concentration levels tested.

Some differences exist between the two tables, notably in

TABLE 2

COMPARISON OF LABORATORY STUDIES WITH NEGATIVE RESULTS WITH THE NIOSH REL's TWA/CEILING LEVELS AND ACGIH TLVs/STELs

Chemical	NIOSH REL (PPM)	ACGIH TLV (PPM)	Exposure (PPM)	Duration ^a	(No Positive Effects at These Concentrations)
					References
Methyl chloride	LFL ^b	50	100	3 hr	Putz-Anderson <i>et al.</i> 1981 [36] Stewart <i>et al.</i> 1977 [52]
		100	100	1, 3, 7.5 hr	
Methylene chloride	LFL ^b	50 ^c	242-964	30 min	Gamberale <i>et al.</i> 1975 [19] DiVincenzo <i>et al.</i> 1972 [13]
		175 ^c	100+200	2-4 hr	
Styrene	50 100	100	50-250	30 min	Gamberale & Hultengren 1974 [18] Stewart <i>et al.</i> 1968 [47]
		100	50-100	2-7 hr	
Trichloroethylene	25	50 200	100+300	2 hr	Vernon and Ferguson 1969 [57] Stewart <i>et al.</i> 1973 ^a [50] Nakaaki <i>et al.</i> 1973 [30] Gamberale <i>et al.</i> 1976 [21] Konietzko <i>et al.</i> 1975 [27] Nomiyama & Nomiyama 1977 [31] Ettema <i>et al.</i> 1975 [14] Winneke 1982 [64]
			110	8 hr	
			100	6 hr	
			100+200	70 min	
			95	4 hr	
			81-201	4 hr	
			150+300	2.5 hr	
			50	3.5 hr	
1,1,1-Trichloroethane	200 350	350 450	350	8 hr	Salvini <i>et al.</i> 1971 [38] Gamberale & Hultengren 1973 [17]
			250	30 min	
Tetrachloroethylene	MWL ^d	50 200	100	5.5 hr	Stewart <i>et al.</i> 1977 [53]
Toluene	100 200	100 150	200	6 hr	Suzuki 1973 [55] Ogata <i>et al.</i> 1970 [33] Gamberale & Hultengren 1972 [16] Winneke 1982 [64] Stewart <i>et al.</i> 1975 [51] Anderson <i>et al.</i> 1983 [3] Dick <i>et al.</i> 1984 [11] Anshelm Olson <i>et al.</i> 1985 [5] Cherry <i>et al.</i> 1983 [10]
			100+200	7 hr	
			100	20 min	
			100	3.5 hr	
			100	3.5-7.5 hr	
			100	6 hr	
			100	4 hr	
			80	4 hr	
			80	4 hr	
			Xylene	100 200	
100-150	4-6 hr				
80	4 hr				
Methyl ethyl Ketone	200	200 300	200	4 hr	Dick <i>et al.</i> 1984 [11]
White spirit	60 310	100 200 ^f	625-2500 ^e	30 min	Gamberale <i>et al.</i> 1975 [20]
FC-113 ^g	—	1000 1250	1500	2 hr 45 min	Stopps and McLaughlin 1967 [54] Reinhardt <i>et al.</i> 1971 [37]
			500+1000	6 hr for 5 days each level	

^aDuration—min=minutes; hr=hours; days.^bLFL—Lowest Feasible Level.^cProposed change in 1986-87 TLVs[®].^dMWL—Minimize Workplace Level.^eValues reported in mg/m³ are converted to approx. ppm.^fSTEL is dropped in the 1986-87 TLVs[®].^gFluorocarbon-113 (1,1,2-Trichloro-1,2,2-trifluoroethane).

the trichloroethylene, 1,1,1-trichloroethane, methylene chloride, xylene and styrene studies. The Salvini [39] study, using trichloroethylene and the more standard psychomotor tests as the neurobehavioral measures, reported a 110 ppm effect level that has never been replicated despite numerous attempts using similar tests [12]. However, a recent study [28] using electronystagmographic measurements of vestibulo-oculomotor responses has reported significant changes in a one-hour exposure at a mean concentration level of 55 ppm coupled with physical exercise (50 watts). The addition of exercise, which increases solvent uptake, probably lowered the threshold of effects using a series of new electrophysiological tests. These tests may be more sensitive indicators of CNS responses than the more standard psychomotor tests. These same authors [25,32] using this research protocol have also reported significant effects using toluene and styrene at concentrations lower than other reports. The 1,1,1-trichloroethane [38] study which reported no effects is at variance with another study reporting significant effects using similar concentrations [17] (see Table 2). In the studies of methylene chloride, similar exposure concentrations have caused marginal decrements as noted by Putz [35] and Winneke [63], but not found by Gamberale [19] and DiVincenzo [13]. There is one styrene [34] study reporting effects at 50 ppm, but two other studies [18,47] using the same concentration level showed no effects. The study demonstrating effects [34] involved a small subject group (five) which, given the lack of replication from other studies, would render the result as questionable. Hence, the 50 ppm effect level for styrene seems unlikely. The two tetrachloroethylene studies [49,53] conflict (one reported effects, the other didn't), even though they were conducted by the same researcher. The latter study [53] reported no effects and should be considered the more definitive one because it included a control condition.

The xylene studies also have some interpretation problems because the neurobehavioral test measurements don't show consistent results, even at the lowest levels of exposure. This is due to the Savolainen reports [41-44] which used fluctuating exposure levels singly and in combination with physical exercise/ethanol conditions. In these studies significant effects were reported at lower levels than have been found for constant single exposure level conditions.

In general, there is little evidence in Table 2 of any acute CNS disturbances, as indicated by behavioral performance tests in humans, at either the present day NIOSH recommended levels or the ACGIH TLV's® for this small number of chemicals tested.

Tables 3 and 4 are presented to indicate the potential for the prevention of neurotoxic effects by using objective neurobehavioral test results. Neurobehavioral methods may provide more sensitive tests to detect sub-clinical and/or early neurotoxic effects in humans. Even these minimal insults to the nervous system may indicate early stages of injury that could eventually progress to fully developed clinical diseases [65].

Table 3 provides a rough calculation of the effect ratios using the present-day NIOSH REL's, the TLVs® and the OSHA PELs. These values are compared to the lowest and highest reported concentration levels demonstrating irritant effects and neurobehavioral deficits. Only the IDLH levels are used for narcotic effects. Concentration levels and effect ratios (in parentheses) reflect special treatment conditions such as fluctuating exposures or the addition of exercise that often result in different values than the sedentary, constant

exposure conditions. These special conditions are identified in the footnotes. To compute effects ratios, concentrations where effects were reported were divided by the recommended NIOSH REL's and ACGIH TLVs® limits and the PEL's, and then rounded to the nearest whole number. Larger effect ratio numbers indicate greater protection from the solvent exposures.

Table 3 indicates considerable differences between the various chemicals on the effect ratios provided by the various exposure limits, both at the average levels (TWAs and TLVs) and the ceiling values and STELs. The NIOSH RELs are the most conservative, followed by the ACGIH TLVs®. Most of the OSHA PEL's, which are the enforceable regulatory limits, have not been updated for 18 years, and this is reflected in the low ratio between the PEL's and the neurotoxic effect levels of some of these chemicals. With some solvents (tetrachloroethylene, methylene chloride, acetone, toluene), the allowable concentrations are at levels where neurobehavioral test effects have been reported. Solvents that have been identified as possible carcinogens or have other known toxic effects (methyl chloride, methylene chloride, tetrachloroethylene, trichloroethylene, styrene) have the lowest recommended levels (for methylene chloride and tetrachloroethylene—NIOSH only) and thus the highest ratios. Tetrachloroethylene is not included in Tables 3 and 4 because only one concentration level has been tested and reported. Six chemicals have low ratios against the effect levels indicated by neurobehavioral test results. Four of these (acetone, fluorocarbon-113, white spirit, and 1,1,1-trichloroethane) are only represented by one study or studies with small sample sizes, which offer(s) a limited basis for definitive conclusions. Further research seems particularly needed here. Toluene and xylene ratios are low, but these two chemicals have been extensively tested at the present TLV® concentrations with no evidence of acute neurotoxic effects.

The safety margins for short term exposure limits (STELs®), which are present in Table 4 indicate some potential for possible neurotoxic effects. For many of the chemicals in this Table, which is organized similarly to Table 3, the effect ratios are low, often less than 1.

The concentrations and chemicals for which neurobehavioral effects are reported at both the high and low concentration levels as occurring at or below the established ceiling levels are methylene chloride, 1,1,1-trichloroethane, tetrachloroethylene, toluene (OSHA only), and acetone. While differences in exposure durations may seem apparent between the 8 hour TWA/TLVs, the NIOSH 10 hour TWA and short duration studies, actual exposure durations experienced at the worksite probably closely approximate the 2-6 hour average experimental exposure conditions.

DISCUSSION

This paper outlines a use of behavioral test data for defining an adequate margin of safety to prevent the onset of acute effects and the possible development of chronic solvent neurotoxicity. Nonetheless, one must not overlook the complexities involved in these determinations. The potential for acute intoxication varies widely among chemicals and individuals, and most exposures in the workplace are combinations involving other chemicals and environmental hazards (heat, noise, dust, ventilation, etc.). Similarly, it would be unwise to extend these conclusions about the range of significant neurotoxic effects indicated by these studies to

TABLE 3
EFFECT RATIOS PROVIDED BY THE RECOMMENDED STANDARDS AND PELs
AGAINST WORKPLACE TWA's

Chemical	Irritant Effects			Neurobehavioral		Narcosis (IDLH) ppm
	TWA ppm	Low ppm	High ppm	Low ppm	High ppm	
Methyl chloride		—	—	150	200	10,000
NIOSH	LFL			—	—	—
TLV	50			3	4	200
PEL	100			2	2	100
Methylene chloride		—	—	200	300	5000
NIOSH	LFL ^a			—	—	—
TLV	50 ^b			4	6	100
PEL	500			<1	<1	10
Styrene		100	200	350(113 ^c)	375	5000
NIOSH	50	2	4	7(2)	8	100
TLV	50	2	4	7(2)	8	100
PEL	100	1	2	4(1)	4	50
Trichloroethylene		50	200	300(55 ^d)	1000	1000
NIOSH	25	2	8	12(2)	40	40
TLV	50	1	4	6(1)	20	20
PEL	100	<1	2	3(<1)	10	10
1,1,1-Trichloroethane		500	1000	350	500	1000
NIOSH	200	3	5	2	3	5
TLV	350	1	3	1	1	3
PEL	350	1	3	1	1	3
Toluene		100	200	240(142 ^e)	300	2000
NIOSH	100	1	2	3(1)	3	20
TLV	100	1	2	2(1)	3	20
PEL	200	<1	1	1(<1)	2	10
Xylene		200	—	300(260 ^f)	400	1000
NIOSH	100	2		3(3)	4	10
TLV	100	2		3(3)	4	10
PEL	100	2		3(3)	4	10
Acetone		200	500	250	500	20,000
NIOSH	250	<1	2	1	2	80
TLV	750	<1	<1	<1	<1	80
PEL	1000	<1	<1	<1	<1	20
FC-113 ^g		500		2500		4500
NIOSH	—	—	—	—	—	—
TLV	1000	<1		3		5
PEL	1000	<1		3		5
White spirit ^h		150	400	760		5000
NIOSH	60	3	6	13		83
TLV	100	2	4	8		50
PEL	500	<1	<1	2		10

Effect Ratio—Reported concentration level divided by the NIOSH REL, ACGIH TLV and OSHA PEL.

^aLowest feasible level.

^bProposed change—1986–87 TLVs[®].

^cApproximate mean concentration (87–139 ppm) with 50w exercise condition.

^dApproximate mean concentration (32–78 ppm) with 50w exercise condition.

^eApproximate mean concentration (126–157 ppm) with 50w exercise condition.

^fApproximate mean concentration (126–400 ppm) with fluctuating exposures.

^gFluorocarbon-113 (1,1,2-trichloro-1,1,1-trifluoroethane).

^hStoddard solvent (values are reported in mg/m³, but have been converted to estimated ppm values for this table).

TABLE 4
EFFECT RATIOS PROVIDED BY THE RECOMMENDED STANDARDS AND PELs
AGAINST CEILING/STEL VALUES

Chemical	Irritant Effects			Neurobehavioral		Narcosis (IDLH) ppm
	Ceiling/ STEL	Low ppm	High ppm	Low ppm	High ppm	
Methyl chloride		—	—	150	200	10,000
NIOSH	LFL ^a			—	—	—
TLV	100 ^s			2	2	100
PEL	200 ^c			<1	1	50
Methylene chloride		—	—	200	300	5000
NIOSH	LFL ^a			—	—	—
TLV	500 ^{sx}			<1	<1	10
PEL	1000 ^c			<1	<1	5
Styrene		100	200	350(113 ^b)	375	5000
NIOSH	100 ^c	1	2	4(1)	4	50
TLV	100 ^s	1	2	4(1)	4	50
PEL	200 ^c	<1	1	2(<)	2	25
Trichloroethylene		50	200	300(55 ^d)	1000	1000
NIOSH		—	—	—	—	—
TLV	200 ^s	<1	1	2(<1)	5	5
PEL	200 ^c	<1	1	2(<1)	5	5
1,1,1-Trichloroethane		500	1000	350	500	1000
NIOSH	350 ^c	1	3	1	1	3
TLV	450 ^s	1	2	<1	1	2
PEL		—	—	—	—	—
Toluene		100	200	240(142 ^e)	300	2000
NIOSH	200 ^c	<1	1	1(<1)	2	10
TLV	150 ^s	<1	1	2(<1)	2	13
PEL	300 ^c	<1	<1	<1(<1)	1	7
Xylene		200	—	300(260 ^f)	400	1000
NIOSH	200 ^c	1		2(<1)	2	5
TLV	150 ^s	1		2(<1)	3	7
PEL		—		—	—	—
Acetone		200	500	250	500	20,000
NIOSH		—	—	—	—	—
TLV	1000 ^s	<1	<1	<1	<1	20
PEL		—	—	—	—	—
FC-113 ^g		500		2500		4500
NIOSH		—	—	—	—	—
TLV	1250 ^s	<1		2		4
PEL		<1		3		5
White spirit ^h		150	400	760		83
NIOSH	60	3	6	13		83
TLV	100	2	4	8		50
PEL	500	—	—	—		—

Effect Ratio—Reported concentration level divided by the NIOSH REL, ACGIH TLV and OSHA PEL.

^aLowest feasible level.

^bApproximate mean concentration (87–139 ppm) with 50w exercise condition.

^cCeiling value.

^dApproximate mean concentration (32–78 ppm) with 50w exercise condition.

^eApproximate mean concentration (126–157 ppm) with 50w exercise condition.

^fApproximate mean concentration (126–400 ppm) with fluctuating exposures.

^gFluorocarbon-113 (see Table 3).

^hStoddard solvent (see Table 3).

^sSTEL.

^{sx}STEL is dropped in the 1986–87 TLVs[®].

other solvents. The number of solvents studied is small and, overall, there are both good and poorly designed studies included in this review. Of equal importance are limitations on the range of neurobehavioral effects studied and the lack of replication (only one study) for many of the solvents. However, the consistency with which certain effects are measured by behavioral performance tests at concentrations below those reported by overt indicators of narcosis represents a potential criterion. Standardized neurobehavioral toxicity test performance measures could provide an objective benchmark for the development of recommended exposure levels. For the CNS effects which have been studied, standardized test performance measures would also allow limits to be established with objectively definable criteria which relate to the possible long term development of solvent neurotoxicity. Although the connection of mild reversible CNS deficits from short-duration exposures with long term development of solvent neurotoxicity is as-yet-unproven, it is a possibility. Some of the same decrements reported after short duration exposures by behavioral testing show more severe impairment after long term chronic exposures. Exposure limits could be adjusted upwards or downwards when coupled with other indicators such as cumulative body burden levels, carcinogenic potential, specific organ toxicity, and physical demands of work in certain job tasks.

SUMMARY

The main points to be concluded from this paper are as follows: (1) Performance changes measured by neurobehavioral tests which occur following controlled short duration exposures are reported at concentrations between those levels which produce irritant and narcotic effects. In most cases the performance decrements are at concentrations closer to the irritant effect levels than the levels where overt narcosis is reported. (2) For the chemicals which have been tested, the performance changes rarely occur below the limits recommended by the standards recommending bodies (NIOSH and ACGIH), but they do occur at some of the currently enforceable levels (PELs). (3) The effect ratios for ceiling/STEL values reveal low margins of protection for several solvents. This may indicate that greater attention needs to be devoted to setting ceiling/STEL values and in the prevention of exposures that exceed them. (4) Neurobehavioral testing may offer promise for testing the potential for long-term development of solvent neurotoxicity from repeated exposures to solvents. In conclusion, it is hoped that this paper will stimulate interest in the use of neurobehavioral tests to expand the criteria presently in use for recommending safe exposure limits for individuals exposed to solvents.

REFERENCES

- American Conference of Governmental Industrial Hygienists. *Documentation of the Threshold Limit Values*, fourth edition, 1980 (and supplemental documentation for 1981-1984). Cincinnati, OH: ACGIH Publications Office (6500 Glenway, Bldg. D-5, zip 45211), 1980, p. 84.
- American Conference of Governmental Industrial Hygienists. *Threshold Limit Values and Biological Exposure Indices for 1986-87*. Cincinnati, OH: ACGIH Publications Office (6500 Glenway, Bldg. D-7, zip 45211), 1986.
- Anderson, I., G. R. Lundqvist, L. Mølhave, O. F. Pederson, D. F. Proctor, M. Vaeth and D. P. Wyon. Human response to controlled levels of toluene in six-hour exposures. *Scand J Work Environ Health* 9: 405-418, 1983.
- Anger, W. K. Neurobehavioral testing of chemicals: Impact on recommended standards. *Neurobehav Toxicol Teratol* 6: 147-153, 1984.
- Anshelm Olsen, B., F. Gamberale and A. Iregren. Coexposure to toluene and p-xylene in man: central nervous functions. *Br J Ind Med* 42: 117-122, 1985.
- Åstrand, I. Editorial: Uptake of solvents from the lungs. *Br J Ind Med* 42: 217-218, 1985.
- Aviado, D. M. and M. S. Micozzi. Fluorine-containing organic compounds. In: *Patty's Industrial Hygiene and Toxicology*, edited by G. D. Clayton and E. F. Clayton. New York: John Wiley & Sons, 1981, pp. 3071-3115.
- Baker, E. L., T. J. Smith and P. J. Landrigan. The neurotoxicity of industrial solvents: A review of the literature. *Am J Ind Med* 8: 207-217, 1985.
- Baker, E. L. and L. J. Fine. Solvent neurotoxicity: the current evidence. *J Occup Med* 28: 126-129, 1986.
- Cherry, N., J. D. Johnston, H. Venables, H. A. Waldron, L. Buck and C. J. Mackay. The effects of toluene and alcohol on psychomotor performance. *Ergonomics* 26: 1081-1087, 1983.
- Dick, R. B., J. V. Setzer, R. Wait, M. B. Hayden, B. J. Taylor, B. Tolos and V. Putz-Anderson. Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. *Int Arch Occup Environ Health* 54: 91-109, 1984.
- Dick, R. B. and B. L. Johnson. Human experimental studies in neurobehavioral toxicology. In: *Neurobehav Toxicol*, edited by Zoltan Annau. Baltimore: Johns Hopkins University Press, 1986, pp. 348-387.
- DiVincenzo, G. D., F. J. Yanno and B. D. Astill. Human and canine exposures to methylene chloride vapor. *Am Ind Hyg Assoc J* 33: 125-135, 1972.
- Ettema, J., L. Kleerekoper and W. C. Duba. Study of mental stresses during short-term inhalation of trichloroethylene. *Staub* 35: 409-410, 1975.
- Ferguson, R. K. and R. J. Vernon. Trichloroethylene in combination with CNS drugs. *Arch Environ Health* 20: 462-467, 1970.
- Gamberale, F. and M. Hultengren. Toluene exposure II. Psychophysiological functions. *Work Environ Health* 9: 131-139, 1972.
- Gamberale, F. and M. Hultengren. Methylchloroform exposure II. Psychophysiological functions. *Work Environ Health* 10: 82-92, 1973.
- Gamberale, F. and M. Hultengren. Exposure to styrene II. Psychological functions. *Work Environ Health* 11: 86-91, 1974.
- Gamberale, F., G. Annwall and M. Hultengren. Exposure to methylene chloride II. Psychological functions. *Scand J Work Environ Health* 1: 95-103, 1975.
- Gamberale, F., G. Annwall and M. Hultengren. Exposure to white spirit II. Psychological functions. *Scand J Work Environ Health* 1: 31-39, 1975.
- Gamberale, F., G. Annwall and B. A. Olson. Exposure to trichloroethylene II. Psychological functions. *Scand J Work Environ Health* 4: 220-224, 1976.
- Gamberale, F., G. Annwall and M. Hultengren. Exposure to xylene and ethylbenzene III. Effects on central nervous functions. *Scand J Work Environ Health* 4: 204-211, 1978.
- Gamberale, F. Use of behavioral performance tests in the assessment of solvent toxicity. *Scand J Work Environ Health* 11: Suppl 1, 65-74, 1985.

24. Horváth, M., E. Frantik and P. Krekule. Diazepam impairs alertness and potentiates the similar effect of toluene. *Act Nerv Super (Praha)* **23**: 177-179, 1981.
25. Hydén, D., B. Larsby, H. Anderson, L. M. Ödkvist, C. Liedgren and R. Tham. Impairment of visuo-vestibular interaction in humans exposed to toluene. *ORL* **45**: 262-269, 1983.
26. Johnson, B. L. and W. K. Anger. Behavioral toxicology. In: *Environmental and Occupational Medicine*, edited by W. Rom. Boston: Little, Brown, 1983, pp. 329-350.
27. Konietzko, H., J. Elster, A. Benesath, K. Drysch and H. Weichardt. Psychomotor reactions under standardized trichloroethylene load. *Arch Toxicol* **33**: 129-139, 1975.
28. Larsby, B., R. Tham, B. Eriksson, D. Hydén, L. Ödkvist, C. Liedgren and I. Bunntors. Effects of trichloroethylene on the human vestibulo-oculomotor systems. *Acta Otolaryngol (Stockh)* **101**: 193-199, 1986.
29. Matsushita, T., E. Goshima, H. Miyakaki, K. Maeda, Y. Takeuchi and T. Inoue. Experimental studies for determining the MAC value of acetone. 2. Biological reactions in the "six-day exposure" to acetone. *Sangyo Igaku* **11**: 507-515, 1979.
30. Nakaaki, K., N. Onishi, H. Iida, K. Kimotsuki, S. Fukabori and Y. Morikiyo. An experimental study on the effect of exposure to trichloroethylene vapor in man. *J Sci Labour* **49**: 449-463, 1973.
31. Nomiya, K. and H. Nomiya. Dose-response relationship for trichloroethylene in man. *Int Arch Occup Environ Health* **39**: 237-248, 1977.
32. Ödkvist, L. M., B. Larsby, R. Tham, H. Ahlstedt, B. Anderson, B. Eriksson and C. Liedgren. Vestibulo-oculomotor disturbances in humans exposed to styrene. *Acta Otolaryngol (Stockh)* **94**: 487-493, 1982.
33. Ogata, M., T. Katsumaro, and Y. Takatsuka. Urinary excretion of hippuric acid and m- or p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- or p-xylene as a test of exposure. *Br J Ind Med* **27**: 43-50, 1970.
34. Oltramare, M., E. Desbaumes, C. Imhoff and W. Michiels. *Toxicology of Styrene Monomer: Experimental and Clinical Research in Man*. Geneva: Medicine & Hygiene, 1974, pp. 84-100.
35. Putz, V. R., B. L. Johnson and J. V. Setzer. A comparative study of the effects of carbon monoxide and methylene chloride on human performance. *J Environ Pathol Toxicol* **2**: 97-112, 1979.
36. Putz-Anderson, V., J. V. Setzer, J. S. Croxton and F. C. Phipps. Methyl chloride and diazepam effects on performance. *Scand J Work Environ Health* **7**: 8-13, 1981.
37. Reinhardt, C. F., M. E. McLaughlin, M. E. Maxfield, L. S. Mullin and P. E. Smith. Human exposures to fluorocarbon 113 (1,1,2-trichloro-1,2,2-trifluoroethane). *Am Ind Hyg Assoc J* **32**: 143-152, 1971.
38. Salvini, M., S. Binaschi and M. Riva. Evaluation of the psychophysiological functions in humans exposed to threshold limit value of 1,1,1-trichloroethane. *Br J Ind Med* **28**: 286-292, 1971.
39. Salvini, M., S. Binaschi and M. Riva. Evaluation of the psychophysiological functions in humans exposed to trichloroethylene. *Br J Ind Med* **28**: 293-295, 1971.
40. Sandmeyer, E. Aromatic hydrocarbons. In: *Patty's Industrial Hygiene and Toxicology*, edited by G. D. Clayton and E. F. Clayton. New York: John Wiley & Sons, 1981, pp. 3253-3431.
41. Savolainen, K. Combined effects of alcohol on the central nervous system. *Acta Pharmacol Toxicol (Copenh)* **46**: 366-372, 1980.
42. Savolainen, K., V. Riihimäki and M. Linnoila. Effects of short-term xylene exposure on psychological functions in man. *Int Arch Occup Environ Health* **44**: 201-211, 1979.
43. Savolainen, K., V. Riihimäki, A. M. Seppäläinen and M. Linnoila. Effects of short-term m-xylene exposure and physical exercise on the CNS. *Int Arch Occup Environ Health* **45**: 105-121, 1980.
44. Savolainen, K., V. Riihimäki and A. Laine. Biphasic effects of inhaled solvents on human equilibrium. *Acta Pharmacol Toxicol (Copenh)* **51**: 237-242, 1982.
45. Savolainen, K., V. Riihimäki, O. Muona, J. Kekoni, R. Luukkonen and A. Laine. Conversely exposure-related effects between atmospheric m-xylene concentrations and human body sense of balance. *Acta Pharmacol Toxicol* **57**: 67-71, 1985.
46. Scheffers, T. M. L., F. J. Jongeneelen and P. C. Bragt. Development of effect-specific limit values (ESLVs) for solvent mixtures in painting. *Ann Occup Hyg* **29**: 191-199, 1985.
47. Stewart, R. D., H. C. Dodd, E. D. Baretta and A. W. Schaffer. Human exposure to styrene vapor. *Arch Environ Health* **16**: 656-662, 1968.
48. Stewart, R. D., H. H. Gay, A. W. Schaffer, D. S. Erley and V. K. Rowe. Experimental human exposure to methyl chloroform vapor. *Arch Environ Health* **19**: 467-472, 1969.
49. Stewart, R. D., E. D. Baretta, H. C. Dodd and T. R. Torkelson. Experimental human exposure to tetrachloroethylene. *Arch Environ Health* **20**: 224-229, 1970.
50. Stewart, R. D., C. L. Hake, A. J. Lebrun, J. H. Kalbfleisch, P. E. Newton, J. E. Peterson, H. H. Cohen, R. Struble and K. A. Busch. *Effects of Trichloroethylene on Behavioral Performance Capabilities*. Cincinnati, OH: DHEW-NIOSH Contract Report No. HSM-99-72-84, 1973.
51. Stewart, R. D., C. L. Hake, H. V. Forster, A. J. Lebrun, J. E. Peterson and A. Wu. *Toluene: Development of a Biological Standard for the Industrial Worker by Breath Analysis*. Cincinnati, OH: DHEW-NIOSH Contract Report No. 99-72-84, 1975.
52. Stewart, R. D., C. L. Hake, A. Wu, S. A. Graff, H. V. Forster, W. H. Keeler, A. J. Lebrun, P. E. Newton and R. J. Soto. *Methyl chloride: Development of a Biological Standard for the Industrial Worker by Breath Analysis*. Cincinnati, OH: DHEW-NIOSH Report No. 77-1, 1977.
53. Stewart, R. D., C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow and M. Vucicevic-Salama. *Effects of Perchloroethylene/Drug Interaction on Behavioral and Neurological Function*. Cincinnati, OH: DHEW-NIOSH Technical Report No. 77-191, 1977.
54. Stopps, G. J. and M. McLaughlin. Psychophysiological testing of human Ss exposed to solvent vapors. *Am Ind Hyg Assoc J* **28**: 43-50, 1967.
55. Suzuki, H. Autonomic nervous responses to experimental toluene exposure in humans. *Sangyo Igaku* **15**: 379-384, 1973.
56. Torkelson, T. R. and V. K. Rowe. Halogenated aliphatic hydrocarbons containing chlorine, bromine and iodine. In: *Patty's Industrial Hygiene and Toxicology*, edited by G. D. Clayton and E. F. Clayton. New York: John Wiley & Sons, 1981, pp. 3433-3601.
57. Vernon, R. J. and R. K. Ferguson. Effects of trichloroethylene on visual-motor performance. *Arch Environ Health* **18**: 894-900, 1969.
58. U.S. Department of Health, Education and Welfare, Public Health Service, *NIOSH Criteria for a Recommended Standard: Occupational Exposure to Ketones*. Washington, DC: DHEW (NIOSH) Publication No. 78-173, 1978.
59. US Department of Health and Human Services, Public Health Service, Centers for Disease Control, *NIOSH Recommendations for Occupational Safety and Health Standards*. Morbidity and Mortality Weekly Report-Supplement. 35(1s), Sept. 26, 1986.
60. US Department of Health and Human Services, Public Health Service, Centers for Disease Control *NIOSH Pocket Guide to Chemical Hazards*. Washington, DC: DHEW (NIOSH) Publication No. 78-210, 1985.
61. US Department of Health and Human Services/US Department of Labor. *NIOSH/OSHA Occupational Health Guidelines for Chemical Hazards*. Washington, DC: DHHS (NIOSH) Publication No. 81-123, 1981.
62. Windemuller, F. B. and J. Ettema. Effects of combined exposure to trichloroethylene and alcohol on mental capacity. *Int Arch Occup Environ Health* **41**: 77-85, 1978.

63. Winneke, G., J. Kastka and G. G. Fodor. Disturbances of vigilance and visual-motor performance resulting from air pollutants and drugs. In: *Adverse Effects of Environmental Chemicals and Psychotropic Drugs*, edited by M. Horvath. Amsterdam: Elsevier, 1973, pp. 193-201.
64. Winneke, G. The behavioral effects of exposure to some organic solvents: Psychophysiological aspects. In: *Occupational Neurology*, edited by J. Juntunen. *Acta Neurol Scand* **66**: Suppl 92, 117-129, 1982.
65. World Health Organization/Commission of the European Communities. *Neurobehavioral Methods in Occupational and Environmental Health: Symposium Report*. WHO Regional Office for Europe, Copenhagen, 1985.