

HUMAN NEUROBEHAVIORAL TOXICOLOGY TESTING: CURRENT PERSPECTIVES

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Standardized tests or test batteries for neurotoxic effects are needed for premarket testing of chemicals (and related regulatory needs) and for the development of a neurotoxicity data base. Three widely known human test batteries based on past research findings and developed to screen for a broad range of neurotoxic effects are currently in use. One was developed by Finland's Institute of Occupational Health, one was recently recommended by the World Health Organization, and one was recently developed as a computer-implemented battery by US researchers. Each of these batteries assesses many frequently occurring neurotoxic effects, but each is limited by the lack of tests for some motor and sensory functions and affective responses that often occur following chemical exposures. Problems with field or worksite assessments using these test batteries involve age, education, socioeconomic, and job differences between exposed and comparison groups, and the lack of normative data on these batteries. To address some of these problems, the human neurobehavioral test batteries are currently undergoing reliability or validity assessments on a national and international scale. This will provide an assessment of their utility and accelerate development of a data base of neurotoxic effects of chemicals.

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2. Key words: neurobehavioral testing, test batteries.

3. Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; EPA, U.S. Environmental Protection Agency; FIOH, Finland's Institute of Occupational Health; NCTB, Neurobehavioral Core Test Battery; NCTR, National Center for Toxicological Research; NES, Neurobehavioral Evaluation System; NIOSH, National Institute for Occupational Safety and Health; NOES, National Occupational Environment Survey; NOHS, National Occupational Hazard Survey; TLV, threshold limit value; WHO, World Health Organization.

INTRODUCTION

Twenty-five years ago, Joseph Ruffin, a staff physician with the Kaiser Steel Corporation, published a call for "Functional Testing for Behavioral Toxicity: A Missing Dimension in Experimental Environmental Toxicology" in the *Journal of Occupational Medicine* (1963). Since that time, the field of behavioral toxicology, or, more broadly, neurotoxicology, has shown a rapid growth and become one of the first independent specialty fields under the general rubric of toxicology. One result of this growth is that sufficient research has accumulated to allow the development of screening programs for behavioral toxicity, the topic toward which this manuscript is directed.

There are two reasons for developing standardized tests or test batteries to screen for (i.e., identify) effects of neurotoxic chemicals: a) premarket testing or related regulatory needs, and b) development of a neurotoxicity data base. While the former reason is a relatively recent development impacting this field, the latter has a longer history. Scientists within the field have encouraged standardization of tests (Morgan and Repko, 1974; Dews, 1975; Buck et al., 1977) and the use of reference chemicals as positive controls (Laties, 1973; Buelke-Sam, 1980). Though never explicitly stated, the reason is to allow us to relate findings in one laboratory to findings in other laboratories, or to relate findings in one country to those in other countries. The ultimate purpose is to develop enough information on a range of chemicals that general principles of neurotoxicity can be gleaned, or that commonalities can be identified. Only then can the chemical-by-chemical approach to testing, now typical in this field, be replaced by a more expeditious approach. To identify the hoped-for commonalities, a data base must be assembled from research on diverse chemicals studied with common methods. This suggests the need to select standard methods to be used in research to identify neurotoxic effects. It is also consistent with the regulatory needs for pre- and post-market screening.

The selection of tests for a neurotoxicity screening battery has occupied the field of neurotoxicology for several years, especially since the Environmental Protection Agency (EPA) asked the field to select neurobehavioral screening tests in 1979. In that year, the EPA sponsored a conference in San Antonio with the purpose of identifying behavioral tests which could be used to evaluate new or untested chemicals for behavioral/nervous system effects, a primary regulatory need regarding TSCA, the Toxic Substances Control Act (Geller et al., 1979). At the end of the meeting, Drs. Weiss and Laties of the University of Rochester summed up their opinion for EPA: "This collection of papers provides the most emphatic statement so far of how essential it is for the Environmental Protection Agency to shun test [selection] standardization. ...A behavioral analog of the Ames test...is an impossible dream." These comments exemplify the strong trend of opinion opposing the development of screening test batteries in the psychology community. This is especially notable among those researchers studying neurotoxic effects in adult animals. Those in the

field of behavioral teratology have been more tractable on this topic, generally adopting test batteries common to several laboratories. The National Center for Toxicological Research (NCTR) collaborative laboratory study established the replicability of one such battery, as described in 1985 (Buelke-Sam et al.). Those scientists conducting human neurobehavioral worksite research have also tackled the problem of battery development with enthusiasm in recent years. Several investigators in the United States are in the process of developing or validating human neurotoxicity test batteries (Otto and Eckerman, 1985).

RATIONALES FOR DEVELOPING TEST BATTERIES

Two rationales can be formulated for selecting tests into a reasonably comprehensive battery of the sort needed to access the range of behavioral changes produced by the variety of chemicals found in the United States. The first and most comprehensive rationale would be to assess all major nervous system functions in order to identify all potential problems that might be produced by chemical exposures. This would require a taxonomy of nervous system functions. While such taxonomies have been developed by Carroll (1980) for cognitive functions and by Fleischman and Quaintance (1984) for a range of performance tasks, there is no widely accepted taxonomy that attempts to specify all nervous system functions. Of course, any such list would be too broad to accommodate in a test battery of reasonable length. The second rationale would be to select tests that would measure neurotoxic effects typically found following occupational or environmental exposures. This rationale for developing a battery of tests is likely to be an evolutionary one. That is, as certain effects replace others as the most frequently reported problems, the make-up of the battery would be altered.

Neither of these approaches has been followed exclusively. Eckerman and others (Gullion and Eckerman, 1986) developed one test battery based on eight cognitive factors identified by Carroll (1980). However, the battery has not been used in field evaluations. On the other hand, several approaches to the development of human neurotoxicity test batteries have been followed, and the resulting test batteries are undergoing field trials. The more prominent approaches will be discussed next.

Finland's Institute of Occupational Health Approach. Historically, the first approach to worksite neurotoxicity testing was developed at Finland's Institute of Occupational Health (FIOH) in the 1950's. Investigators at FIOH developed a test battery that is well adapted to studying the main concerns in Finnish industry, particularly exposure to a limited number of solvents. Their tests (Table 1), which have been streamlined through factor analysis over the years, reflect various psychological domains which are also seen in Table 1 (Hänninen and Lindstrom, 1979). The battery is now used routinely in neurotoxicity evaluations of worker groups in Finland, including prospective studies involving new workers.

TABLE 1
Finland's Institute of Occupational Health (FIOH) Test Battery

<u>Test</u>	<u>Domain</u>
Benton Visual Retention	Visual Perception
Bourdon-Wiersma	Visual Perception
Symmetry Drawing	Visual Perception
Mira Test	Motor Performance
Reaction Time	Motor Performance
Santa Ana	Motor Performance
Wechsler Memory Scale (portions)	Cognitive/Memory
Wechsler Adult Intelligence Scale (portions)	Cognitive

Source: Hanninen and Lindstrom, 1979.

Problem-Based Approach. The problem-based approach to worksite testing has its origins in the wide variety of neurobehavioral problems and neurotoxic chemicals found in the United States, where field investigators have typically adopted a unique battery of tests for each particular situation. The tests have been selected based on two factors: (1) the type of symptoms reported by the exposed group to be tested, and (2) the established neurotoxic effects of the chemical under study and/or structurally related chemicals. This general approach has led to the use of literally hundreds of different tests in various worksite studies conducted over the years (Johnson and Anger, 1983), and has also been characteristic of National Institute for Occupational Safety and Health (NIOSH) research (Anger, 1985).

World Health Organization-Recommended Approach. A third approach represents a melding of the first two approaches, and was well articulated in the World Health Organization (WHO) meeting held in Cincinnati during May of 1983. At that meeting, a small group of established researchers in neurotoxicology recommended a core set of tests (the Neurobehavioral Core Test Battery, or NCTB) that could be used as a basic screen to identify a broad range of neurotoxic effects, particularly for use in developing countries. Tests selected into the core set: a) had been used successfully in worksite studies (i.e., they had identified group differences produced by chemical exposures), b) were portable, c) required minimal training to administer them, and d) were expected to be valid and reliable in most cultures. Most of the core tests (Table 2) were well-known "paper and pencil" tests specifically chosen to avoid mechanical or other instrumentation problems (a special concern in developing countries). For the one test requiring a source of electricity (the reaction time test), the instrument selected can be run using batteries as well as 110- or 220-volt current.

TABLE 2
World Health Organization Neurobehavioral Core Test Battery

<u>Test</u>	<u>Functional Domain</u>
Santa Ana	Manual Dexterity
Aiming	Motor Steadiness
Simple Reaction Time	Attention/Response Speed
Digit Symbol	Perceptual-Motor Speed
Benton Visual Retention Test	Visual Perception/Memory
Digit Span	Auditory Memory
Profile of Mood States (POMS)	Affect

Source: Johnson, 1987.

Another series of tests was identified as supplemental to the core battery. Their use was to be dependent on the chemical involved, the type of personnel available to conduct the tests, and the setting in which the tests were to be administered. The core set of tests was intended to generate more uniform, more consistent data from a broad variety of occupations and neurotoxic exposure conditions. The supplemental tests were intended to provide more in-depth information based on the known effects of the chemical under study and symptoms reported by the exposed workers (Johnson, 1987).

Neurobehavioral Evaluation System Approach. The Neurobehavioral Evaluation System (NES) implemented several neurobehavioral tests that have been used successfully in clinical settings and/or in previous field studies on IBM-PC^R and Portable Compaq^R computers. Some 17 tests were available on the NES as of 1986 (Letz and Baker). The tests are listed in Table 3, along with the functions assessed. Tests are frequently added to this battery (the most recent version includes three additional tests not found in Table 3),^a which is following an evolutionary course dictated by current interest in the field. The NES includes variants of five of the seven WHO NCTB tests (noted by asterisks in Table 3). As with the problem-based model, the developers of the NES recommended that the user "select tasks which are appropriate for specific exposure situations" (Baker et al., 1985).

Each of the four approaches described above is pragmatically based, and each used past research findings in selecting tests. Three approaches (FIOH, WHO NCTB, NES) involve a limited battery of tests, and each battery is sensitive to important

^aCurrent information on this battery and the software to implement it are available from Dr. Richard Letz; Assistant Professor, Environmental Sciences Lab, Mt. Sinai School of Medicine, 10 East 102nd Street, New York, NY 10029.

TABLE 3
Computer-Administered Neurobehavioral Evaluation System

<u>Test</u>	<u>Function</u>
Psychomotor Performance	
Symbol-Digit *	Coding speed
Hand-Eye Coordination	Coordination
Simple Reaction Time *	Visuomotor speed
Continuous Performance Test	Attention/Speed
Finger Tapping	Motor speed
Perceptual Ability	
Pattern Comparison	Visual perception
Memory and Learning	
Digit Span *	Short-term memory/attention
Paired-Associate Learning	Visual learning
Paired-Associate Recall	Intermediate memory
Visual Retention *	Visual memory
Pattern Memory	Visual memory
Memory Scanning	Memory processing
Serial Digit learning	Learning/Memory
Cognitive	
Vocabulary	Verbal ability
Horizontal addition	Calculation
Switching attention	Mental flexibility
Affect	
Mood Test *	Mood

*Variant of WHO core test.

Source: Letz and Baker, 1986.

physiological functions. However, none of the batteries aspires to assess the broad range of human functions which was proposed as one basis for test selection above. Further, it is not clear if the functions assessed by these batteries are representative of the range of functions that might potentially be affected by neurotoxic chemicals, the other basis for test selection noted above.

To assess how well these batteries would detect the health effects typically caused by neurotoxic chemicals at low concentrations (i.e., target organ effects), the target organ health effects identified in the research literature will be described, followed by a

comparison of the potential of the test batteries to identify those effects. Since the batteries do not assess the broad range of human functions, it is important to consider how effectively they assess health effects frequently caused by neurotoxic chemicals. There is no direct evidence on this point. Several threads of evidence do, however, provide the data to begin such an assessment. These threads, to be discussed in order below, demonstrate that: a) a large number of chemicals produce effects on the nervous system, and 65 of these chemicals have exposure populations in excess of one million, and b) many nervous system-related health effects occur at lower exposure concentrations than most other effects for certain chemicals.

TARGET ORGAN EFFECTS

Neurotoxic Chemicals. Of the 60,000 (Reiter, 1980) to 100,000 (NIOSH, 1983) chemicals in commerce today, how many affect the nervous system? Anger and Johnson (1985) have reviewed major secondary reference sources in this field (Spencer and Schuamburg, 1980; Clayton and Clayton, 1981, 1982; Gosselin et al., 1976; Lazerev and Levina, 1976; Weiss, 1978; Damstra, 1978; Norton, 1975, 1980; ACGIH, 1980-2) to identify chemicals for which there is evidence of nervous system effects. That chapter identified just over 750 chemicals or chemical groups for which there is evidence of direct or indirect nervous system effects (Anger and Johnson, 1985). It is clear that there are a large number of industrial chemicals that affect the nervous system adversely.

Exposure Populations. There is also evidence that people are exposed to those chemicals. In US workplaces, the National Occupational Hazard Survey (NOHS) identified 200 chemicals, each of which had an estimated 1 million or more persons exposed. These estimates are based on statistical extrapolation from extensive sampling data, and have been published by NIOSH (1977). The number of workers exposed to each chemical is very likely inflated due to the exposure identification strategy of that survey. (The strategy was to list chemicals in work environments whether or not there was indication of actual use or exposure.) It is also obvious that many of the people in that survey were exposed to multiple chemicals, and were thus counted for more than one chemical. (A more recent national survey conducted by NIOSH, the National Occupational Environmental Survey [NOES], is not yet published, but its results are expected to modify this picture considerably.)

Cross-referencing the 750 chemicals noted above that affect the nervous system (Anger and Johnson, 1985) with the 200 chemicals to which 1 million or more people are exposed by NIOSH (1974) estimate indicates that, 65 of the 200, or about one third, are also found in the list of 750 (Anger, 1986). From these data, it is possible to conclude that a large number of US workers work with chemicals which are known to affect the nervous system. These and other factors have led NIOSH to identify

neurotoxic disorders as one of the ten leading occupational problems in the US (CDC, 1983, 1986), and to focus efforts on their prevention.

Behaviors Affected by Many Chemicals. The review that identified 750 chemicals which affect the nervous system also provided an indication of the universe of nervous system-related effects that are known to be produced by industrial chemicals. The various behavioral deficits induced by industrial chemicals were categorized into some 120 nervous system-related effects (Anger and Johnson, 1985). Behavioral effects that have been reported as caused by 25 or more of the 750 chemicals are listed in Table 4, along with the number of chemicals with which each has been linked (in the columns labelled "of 750"). Some of the effects are vague, others are specific. Despite the lack of parallelism, which is quite predictable given the diversity in the source reports, Table 4 contains the 35 behavioral effects most frequently recognized and reported in the reference literature as occurring following exposure to industrial chemicals (Anger, 1986).

This collection of effects provides one measuring stick against which to judge the available test batteries. However, it is not clear if these neurotoxic effects are realistic concerns in the industrial environment. This would be the case if they occur at relatively low exposure levels. That is, are they target organ effects, or health effects that occur at the lowest concentrations relative to other effects for a given chemical, rather than curiosities that occur only at high exposure concentrations. One line of evidence suggesting that they are target organ effects is the fact that these are cited as the basis for recommending workplace standards by one federal agency and one independent professional group.

NIOSH Recommendations. Over the years, NIOSH has produced 91 criteria documents on chemicals/chemical groups/physical agents (counting only once those documents that have been revised), under its mandate in the Occupational Safety and Health Act (1970). These documents provide a review of the literature and recommend exposure maxima. The basis for the recommendation is explicitly stated in each document. A review of those documents indicates that nervous system effects have been an explicitly stated basis in 36 or about 40% of them. Generally, the nervous system effect was identified as one that occurred at very low concentrations and can be described as a target organ effect. The chemical/physical agents are listed in Table 5.

ACGIH Recommendations. In the United States, the earliest national source of recommended limits for exposures to industrial chemicals has been the publications of the American Conference of Governmental Industrial Hygienists (ACGIH). They have published reviews of a far larger number of chemicals than has NIOSH or any other group, and their recommendations will be discussed at some length, as their stated intent is to be comprehensive in reviewing toxic chemicals in commerce in the US (ACGIH, 1982).

The ACGIH's recommendations are provided by their Threshold Limit Value (TLV) committee, composed of voting practitioners from academia and government. Per-

TABLE 4
Neurobehavioral Effects Reported Following Exposures to 25 or More Chemicals

<u>Motor</u>	OF 750	ACGIH ONLY 3*	<u>General</u>	OF 750	ACGIH ONLY
Activity changes	32*	3*	Anorexia	158	15
Ataxia	89	4	Autonomic dysfunction	26	0
Convulsions	183	18	Cholinesterase inhibition	64	26
Incoordination/un- steadiness/clumsiness	62	10	CNS depression	131	10
Paralysis	75	9	Fatigue	87	0
Pupil size changes	31	2	Narcosis/stupor	125	28
Reflex abnormalities	54	0	Peripheral neuropathy	67	36
Tremor/twitching	177	19			
Weakness	179	12			
<u>Sensory</u>			<u>Affect/Personality</u>		
Auditory disorders	37	2	Apathy/languor/lassitude/ lethargy/listlessness	30	15
Equilibrium changes	135	20	Delirium	26	2
Olfaction disorders	37	2	Depression	40	6
Pain disorders	64	7	Excitability	58	9
Pain, feelings of	47	2	Hallucinations	25	2
Tactile disorders	77	5	Irritability	39	4
Vision disorders	121	12	Nervousness/tension	29	11
			Restlessness	31	0
			Sleep disturbances	119	9
<u>Cognitive</u>			[Less than 25 of the 850]		
Confusion	34	0	Nystagmus		2
Memory problems	33	3	Rigidity		3
Speech impairment	28	0	Anxiety		4
			Asthenia		2
			Mental Disorders		6
			CNS Stimulation		4

*Denotes number of chemicals for which effect has been reported.

Adapted from Anger and Johnson, 1985; Anger, 1984; Anger, 1986.

sons from NIOSH and industry serve as non-voting consultants. The ACGIH publishes annually a list of the chemicals most frequently encountered in industry for which there is documented evidence of untoward symptoms or occupational disease. For each chemical listed, they offer recommended exposure maxima, termed Threshold Limit Values (TLVs^R) (ACGIH, 1982), based on the relevant literature and the personal experience of the members and consultants.

The ACGIH recommended TLVs^R for 588 chemicals in 1982 (ACGIH). To support these recommendations, the ACGIH also published a book of Documentation (ACGIH, 1980-1982), which describes the basis for each recommended TLV. Anger (1984) abstracted 36 organ systems, health effects, or other bases which are cited in the

TABLE 5
Agents/Classes Cited by NIOSH Criteria Documents as Producing
Nervous System Effects at Low Concentrations

CHEMICALS/AGENTS	DOCUMENT NO.	CHEMICALS/AGENTS	DOCUMENT NO.
Acrylamide	(77-112)	Methyl alcohol	(76-148)
Alkanes	(77-151)	Methyl parathion	(77-106)
Anesthetic gases, waste	(77-140)	Methylene chloride	(76-138)
Carbaryl	(77-107)	Nitriles	(78-212)
Carbon disulfide	(77-156)	Noise	(HSM 73-11001)
Carbon monoxide	(HSM 73-11000)	Parathion	(76-190)
Carbon tetrachloride	(76-133)	Petroleum solvents, refined	(77-192)
Chloroform	(75-114)	Styrene	(83-119)
Cresol	(78-133)	Tetrachloroethane (perchloroethane)	(76-185)
Dinitro-o-cresol	(78-131)	1,1,2,2-Tetrachloroethane	(77-121)
Ethylene dibromide	(77-221)	Thiols (n-Alkane Mono Thiols,	(78-213)
Fluorocarbon polymers,	(77-193)	Cyclohexanethiol, Benzenethiol)	
decomposition products		Toluene	(HSM 73-11023)
Formaldehyde	(77-126)	1,1,1-Trichloroethane (methyl	(76-184)
Hydrogen cyanide and Salts	(77-108)	chloroform)	
Hydrogen sulfide	(77-158)	Trichloroethylene	(HSM 73-11025)
Ketones	(78-173)	Tungsten and cemented tungsten	(77-127)
Lead, inorganic/revised	(78-158)	products	
Malathion	(76-205)	Xylene	(75-168)
Mercury, inorganic	(HSM 73-11024)	Zinc oxide	(76-104)

Source: NIOSH Criteria Documents.^b

Documentation as the most relevant information leading to the ACGIH recommendations. These presumably reflect those effects produced by low exposure concentrations. Considering only those categories labelled nervous system, unpleasant taste/odor, and eye (other than irritation), a total of 167 chemicals (roughly 1/4 of the total 588) listed through 1982 (ACGIH, 1980-1982) have TLV's based on these direct neurologic or behavioral effects (Anger, 1984). This, and the NIOSH criteria documents, suggest that the nervous system is an important target organ for industrial chemicals in use today.

To return to the 35 effects in Table 4 (produced by 25 or more of the 750 chemicals), most are also found cited under at least two chemicals in the ACGIH Documentation. Thus, most of the effects in Table 4 may be presumed to occur following low-concentration exposures. An additional six effects, which were cited at least two times by ACGIH but less than 25 times in the list of 750, are listed at the bottom on the right side of Table 4. Those effects cited by ACGIH as caused by only one chemical are not included in this Table.

^bNIOSH Criteria documents for each chemical listed in the Table are available by document number (in parentheses) from: NIOSH Publications, 5555 Ridge Ave., Cincinnati, OH 45213.

POTENTIAL OF TEST BATTERIES TO ASSESS TARGET ORGAN HEALTH EFFECTS

The data in Table 4 provide a sample of health effects occurring frequently following exposures to toxic industrial chemicals. How effectively would the test batteries noted above identify or screen for these frequently-occurring effects? The 35 health effects produced by 25 or more chemicals have been repeated in Table 6, in a single column. Table 6 also identifies the tests in the WHO, FIOH, and NES batteries which would presumably assess the various effects, assuming adequate sensitivity of each test and an adequate sample size.

As can be seen in Table 6, many of the motor changes would be identified by the three test batteries, and the POMS or mood tests found in two of the batteries would detect changes in affect. Sensory changes would be poorly identified, as would ataxia and weakness, two effects that occur frequently after toxic chemical exposure. The forte of the batteries, cognitive testing (particularly memory), is aimed at central nervous system (CNS) functions. This is based on the assumption that such effects are not reported very frequently because they are only rarely assessed with any degree of sophistication. This assumption is somewhat substantiated by past worksite research with carbon disulfide, mercury, lead, and methyl chloride. That research has identified subtle CNS deficits in worker groups exposed to concentrations that did not produce peripheral effects or other signs of frank poisoning (Anger and Johnson, 1985). Human laboratory research on acute exposure effects of many solvents also supports this assumption (Dick and Johnson, 1986).

The WHO NCTB, FIOH, and NES test batteries are reasonable, defensible, research-based approaches to the assessment of neurotoxic chemicals. Further, each battery tests for well-established health-related effects that have been accepted by the public health community in the past. They also include tests aimed at assessing the more subtle CNS deficits that occur at lower exposure concentrations than do the more frank poisoning effects that have been the focus of attention in the past.

There are clearly limitations to these batteries, however. The WHO NCTB and FIOH batteries use a test of motor performance (the Santa Ana) that has previously demonstrated differences between a group exposed to toxic chemicals and an unexposed group, but the NES hand-eye coordination test has not yet identified chemical effects. Also, only the FIOH battery and the WHO NCTB have more than one test of coordination. The WHO NCTB is slightly superior to both the NES and FIOH batteries in its use of the POMS test. The FIOH battery has no test for affect, and the NES uses a mood test that is based on the 65-item POMS, but employs only 25 of those items to identify five of the six factors (all but vigor) on the POMS. The reliability and validity of the resulting test has not been assessed thoroughly, and an item by item analysis of the mood test indicates that it does not appear to assess some types of affect that are assessed by the POMS (and occur frequently following chemical exposures). Overall, this assessment would suggest that the WHO battery is

TABLE 6
Neurobehavioral Effects Reported Following Chemical Exposures

<u>750</u>	<u>ACGIH</u>	<u>NEUROBEHAVIORAL EFFECTS</u>	<u>WHO</u>	<u>TESTS</u>	<u>NES</u>	<u>FIOH</u>
		<u>Motor</u>				
32	3	Activity changes				
89	4	Ataxia				
183	18	Convulsions				
62	10	Incoordination/unsteadiness/clumsiness	Santa Ana+	H-E Coord		Santa Ana+
75	9	Paralysis	Santa Ana+	H-E Coord		Santa Ana+
35	2	Pupil size changes				
54	0	Reflex abnormalities				
177	19	Tremor/twitching	Santa Ana+	H-E Coord		Santa Ana+
179	12	Weakness				
		<u>Sensory</u>				
37	2	Auditory disorders				
135	20	Equilibrium changes				
37	2	Olfaction disorders				
64	7	Pain disorders				
47	2	Pain, feelings of				
77	5	Tactile disorders	Santa Ana			Santa Ana+
121	12	Vision disorders	Benton+	Pattern+		Benton+
		<u>Cognitive</u>				
34	0	Confusion	+	+		+
33	3	Memory problems	Benton+	Pattern+		Benton+
28	0	Speech impairment				
		<u>Affect/Personality</u>				
30	15	Apathy/languor/lassitude lethargy/listlessness	POMS	Mood test		
26	2	Delirium				
40	6	Depression	POMS			
58	9	Excitability	POMS			
25	2	Hallucinations				
39	4	Irritability	POMS	Mood test		
29	11	Nervousness/tension	POMS	Mood test		
31	0	Restlessness	POMS			
119	9	Sleep disturbances				
		<u>General</u>				
158	15	Anorexia				
26	0	Autonomic dysfunction				
64	26	Cholinesterase inhibition				
131	10	CNS depression				
87	0	Fatigue POMS				
125	28	Narcosis/stupor	+	+		+
67	36	Peripheral neuropathy	Santa Ana+	H-E Coord		Santa Ana+
*	36	Pathology				
25	2	Psychic disturbances				

*Not included as "behavioral."

†Multiple tests assess this effect.

slightly superior to the FIOH and NES batteries, based on the criteria proposed above. However, the NES has the advantage of being administered by computer,

which reduces administration costs substantially. On the negative side, some of the most frequently-occurring neurotoxic effects, particularly some forms of peripheral neuropathy and affective symptoms, weakness, ataxia, and sensory effects, would be missed by all of the batteries. Of course, it is quite possible that CNS changes are correlated with some of these effects and these tests would thus perform their function of detecting health effects. A "screening" battery is developed for detection, not characterization.

The established test batteries must undergo constant scrutiny. An evolutionary course of test battery development is essential when the battery is based on established health effects, because these effects may change as chemicals in use change. Further, the immense range and diversity of behavior noted above suggests that simple test batteries are inadequate for comprehensive screening. There is the danger of not detecting those effects for which the batteries lack tests. One hopes that the recently-recommended test batteries noted above are designed for the problems of the future by assessing more subtle CNS effects rarely tested adequately in the past.

METHODS DEVELOPMENT EFFORTS UNDER WAY

The test batteries described above are not without their problems. One major problem lies in interpreting the results of these batteries. The neurobehavioral tests in the various test batteries, with only a few exceptions, are not clinical instruments. They do not have established norms based on extensive population testing. Rather, they are performance tests that provide objective measures ideally suited to test-retest (before-after) assessments. Of course, there are never any baseline (pre-exposure) performance data on workers exposed to chemicals. Performance data on the same tests administered to unexposed people must be used for comparison. That is, performance effects are defined, not by established norms, but by comparison data from people believed to be healthy—a referent or control group.

An appropriate control group should consist of people who are not only unexposed to toxic chemicals, but are also similar to the exposed subjects in terms of age, education, job activities or movements, and socioeconomic variables. This is extremely difficult to achieve, and field researchers are virtually always concerned with the accuracy of the controls as a basis for judging the performance of the exposed group. The most pervasive problem in judging the validity of group differences has been age differences between exposed and comparison groups. Therefore, the World Health Organization has recommended the development of normative data from unexposed or control subjects in five age ranges for the NCTB. This recommendation may be extended to the other major neurotoxicity screening batteries. The five arbitrarily selected age ranges are: 16-25, 26-35, 36-45, 46-55, and 56-65. Ideally, the subjects would be employees with occupations relatively typical of those found throughout the country (or at least not atypical), and with a fairly homogeneous educational background. NIOSH is conducting such a study using the NES and the NCTB.

It is the World Health Organization's intention to carry out an assessment of the NCTB in eight nations (WHO, 1987).^c Since the NCTB tests were developed in Western European-derivative countries (primarily Finland and the US), the assessment is aimed at comparing the results from the US and European countries with results from culturally diverse people from different countries. As of this writing, some 15 research groups had applied to participate in the assessment, although some cultural groups are not represented. If test performance in various countries/cultures is within certain ranges, the WHO NCTB battery can be used to assess poisoning incidents or other neurotoxic exposures worldwide, and the results can be generalized to people throughout the world. Thus, data from all countries could be used to assess safe exposure concentrations of specific chemicals. This is intended to accelerate the development of a data base of chemical effects through the use of common tests. It will, in turn, advance the process of identifying chemical classes or mechanisms associated with neurotoxicity, and thus lead to the ultimate goal of prediction of neurotoxicity, rather than identification through *post hoc* discovery of adverse health effects in humans.

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