

ORGANIC SOLVENTS AND TIME-DEPENDENT SENSITIZATION

ŚLAWOMIR GRALEWICZ

Department of Toxicology and Carcinogenesis
The Nofer Institute of Occupational Medicine
Łódź, Poland

Key words: Multiple chemical sensitivity, Time-dependent sensitization, Organic solvents

Abstract. The nervous system is main target of the toxic action of most of organic solvents. There is little doubt that occupational solvent exposure may result in persisting neurobehavioural disturbances – the organic solvent syndrome. Recently, the solvents are quoted among possible causes of the abnormal condition referred to as multiple chemical sensitivity (MCS), and which is characterized by a psychosomatic overreactivity to a variety of chemicals present in food or ambient air. According to some authors, MCS is a manifestation of the time-dependent sensitization (TDS), a phenomenon of progressive increase in responsiveness to chemical agents following acute or intermittent exposure, and related to some functional aberrations within limbic structures. TDS is commonly induced by psychostimulant drugs. The purpose of the present paper was to show, based on the literature data, that under circumstances of acute and repeated exposure, some solvents (mainly toluene) exert effect on behaviour and on the functional state of some neurotransmitter systems similar to that exerted by drugs known to induce TDS. Of special importance is the fact that in case of solvents the behavioural and biochemical changes suggestive of sensitization appear after exposure at levels close to those admissible in the occupational exposure, and that the concentration-effect relationship is nonlinear (an inverted U curve). To date, however, only a few of the existing data may be regarded as a direct evidence of the solvent-induced TDS. It is mainly due to the fact that the experimental protocol of a TDS study does not match the experimental routine of neurotoxicity assessment. Some data suggest that some solvents are possibly unable to induce TDS. The necessity to assess the commonly used solvents for their ability to induce TDS has been emphasized.

The risk of long-term health consequences resulting from occupational and environmental exposure to toxic chemicals is nowadays a problem of great concern for occupational medicine and for the regulatory agencies. Volatile organic solvents occupy the top of the list of such chemicals due to their production volume, multitude of occupational and nonoccupational applications, the route of entry into the organism and the easiness of absorption and tissue penetration.

The primary place of toxic action of organic solvents, typically aliphatic and aromatic hydrocarbons, is the central nervous system (CNS). Some epidemiological studies and case reports suggest that occupational exposure to these compounds may result in persistent neurobehavioural impairments, referred to as 'organic solvent syndrome' (OSS). Consequently, in some countries OSS has been acknowledged as an occupational disease (39,56). For some time now, solvents have been also mentioned as suspected aetiologic factors in multiple chemical sensitivity (MCS), an illness with incidence which, in some highly developed countries, has alarmingly increased (8,38).

MCS is a chronic condition which is manifested by the occurrence of a symptom complex after exposure to a variety of chemicals present in food or ambient air at concentrations which, according to our current knowledge, should produce no harmful effects. The development of MCS is a two-stage process: initiation by an acute, high-level exposure or repeated low-level exposure to a chemical, and elicitation of symptoms by the same substance or a variety of other related and unrelated chemicals (Fig. 1). The symptom variability is very high. Usually, symptoms suggestive of an involvement of the central nervous system dominate. They include concentration-attention and memory failure, fatigue, tiredness, depression, dizziness, somnolence during day hours, derealization, irritability and anxiety. Somatic symptoms, such as muscle and joint pains, digestive problems, weakness, headaches, sinusitis and nasal allergies are also common (7,11).

Stage I: Initiation

Time passing by

Stage II: Elicitation

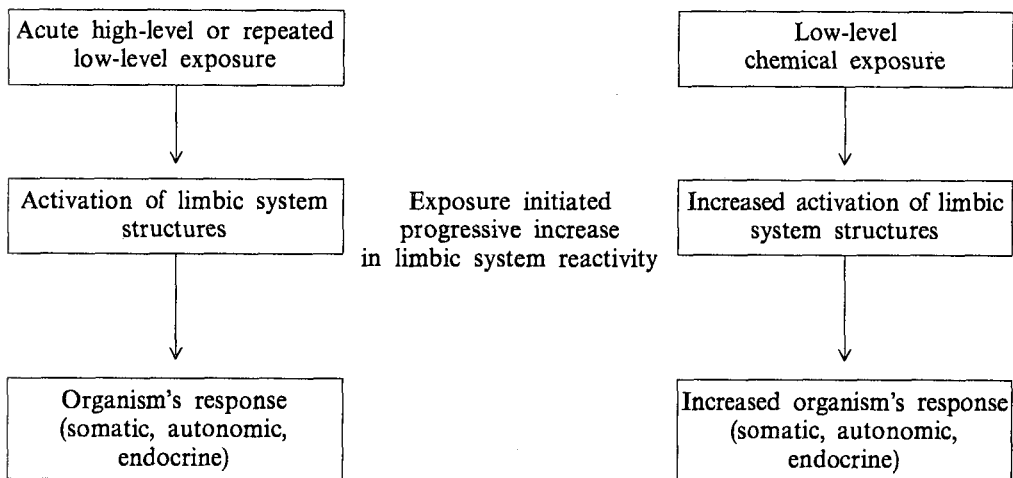


Fig 1. Two-stage process in the development of multiple chemical sensitivity. The arrows do not refer to any known neuronal pathway but denote the succession of events. At stage I, an acute high level or repeated low-level exposure to a chemical results in a direct or indirect activation of limbic system structures. Limbic system activation prompts the appearance of somatic, autonomic and endocrine response (symptoms) and initiates the process of a gradual increase in the limbic system reactivity (a kindling-like phenomenon). Owing to that, at stage II a low-level exposure to a chemical induces a disproportionately large response (7).

The involvement of solvent exposure in the MCS aetiology is suggested by the medical histories (self reports) of patients with MCS diagnosis. According to Miller and Mitzel, for example, 75 out of 112 MCS patients attributed the beginning of their illness to remodelling of a building which commonly involves exposures to mixtures of solvents released from fresh lacquers, paints and glues (40). Besides, some authors found that over 50% solvent-exposed industrial workers manifested symptoms of illness in the presence of a chemical odour (42,50).

The increasing prevalence of the MCS cases raises concern not only among medical personnel but also among toxicologists (mainly neurotoxicologists) and regulators responsible for setting hygiene standards (occupational and environmental exposure limits). As already mentioned, in the MCS patients symptoms of disabling severity may be triggered by exposure levels which, according to the existing standards, should produce no harmful effects. Thus, either the symptoms result from an action of additional exposure-related factor, or some important aspects of the toxic action of a given substance have been overlooked, and not taken into account while testing its toxicity and, consequently, setting the standards of exposure. According to some authors, the symptoms in MCS patients are being triggered by fear of possible harmful effects of exposure rather than by the exposure itself. According to others, MCS may be explained in terms of the Pavlovian conditioning. In the latter case, MCS may be regarded as a result of the association between the odour or taste of a chemical substance and an aversive state which may, but not necessarily, be induced by this substance (10,51). Another hypothesis claims that MCS is a manifestation of time-dependent sensitization (TDS) of limbic structures and pathways responsible for regulation of attention/memory affect visceral and endocrine functions (7,54). TDS is related with the phenomenon of the progressive increase in responsiveness to a variety of stimuli after an acute or repeated, intermittent exposure to a chemical, pharmacological, physical or psychological stressor (3,5,52).

Numerous experimental studies have confirmed that TDS can be induced by the systemic or central administration of variety of drugs (9). The question is whether exposure to a solvent (or solvents) can sensitize the subject — at the neuronal and behavioural levels — to other chemical stressors including the solvent itself. The existing data from experimental animal studies and some clinical observations make this possibility a likely one.

Most of the existing experimental data on TDS come from research into psychostimulants, mainly amphetamine. On the other hand, the majority of the experimental animal studies of solvent neurotoxicity concerns toluene, a representative of aromatic hydrocarbons which are common constituents of industrial solvent mixtures. There are important similarities between the neurobehavioural effects of amphetamine and toluene which explains why toluene, like amphetamine, is the substance of abuse. In the adult rat, the most evident behavioural response to a low dose (up to 2 mg/kg) of amphetamine is an increase in locomotion (36,49). The same effect is produced by toluene, and several other solvents (12,17), administered systemically at low doses or in the course of a low-level inhalation exposure. Moreover, like amphetamine, toluene possess rewarding properties (62), and affects behavioural performance in some test situations much in the same way as amphetamine does (18). At high doses, however, acute effects of toluene and other volatile organic solvents differ markedly from those produced by amphetamine.

Whereas the former produces behavioural depression and narcosis (24,63), the latter produces stereotypes (49), a behaviour regarded by some authors as a way of coping with excessive excitation (41).

The psychostimulant effect of amphetamine is commonly linked with the influence of this drug on the catecholaminergic systems. Apart from being a monoamine oxidase (MAO) inhibitor, amphetamine prompts the release of dopamine from dopaminergic terminals (28).

The locomotion-stimulating effect of this drug is due to an enhanced dopaminergic transmission in the striatum (13,31). It has been demonstrated in numerous studies that exposure to organic solvents affects functioning of the catecholaminergic systems especially the dopaminergic one (Table 1). Generally, the data suggest an increased dopaminergic activity during the exposure to solvents which might account for the locomotion stimulating phase in the effect of such an exposure. Surprisingly, Kondo et al. (33) found that intraperitoneal injection of 800 mg/kg toluene, while producing a significant increase in locomotor activity, did not affect the extracellular levels of dopamine and its metabolites. It was in contrast to methamphetamine (1.0 mg/kg) which stimulated locomotion and increased the extracellular dopamine level. However, it has recently been found that in the presence of remoxipride, a selective D2-dopamine antagonist, toluene-induced hyperactivity was reduced by more than 50% (47). According to the authors, their results clearly show that toluene induces locomotor hyperactivity through a dopamine-dependent mechanism.

It appears from the above data, that toluene, and possibly other volatile solvents, are able to activate the dopaminergic system, i.e. the same system which is being activated by the psychostimulant amphetamine. Activation of the dopaminergic system plays a crucial role in the triggering the sensitization process (30,52,57).

In the studies of TDS, the experimental procedure consists in a pretreatment of animals once or, more commonly, repeatedly over several days with a dose of the substance under study and then, after an interval of several days or weeks, testing the animal behavioural response to a challenge dose of the same substance, or another stressor (to test cross-sensitization). Sensitization is said to occur when the behavioural response to the pharmacological challenge is higher in the animals pretreated with the studied chemical than in the animals pretreated with the vehicle. Such an increased response is a typical outcome of pretreatment with psychostimulants like amphetamine or cocaine (49). In many instances cross-sensitization was reported: animals pretreated with a psychostimulant showed an increased behavioural response to other pharmacological or physical stressors (3,4). The neuronal background of TDS is not well understood (52). Nevertheless, there seems to be a general agreement that the psychostimulant-induced sensitization is a form of neuronal adaptive response to a transient dopaminergic overstimulation, and that the net result of these adaptations is a long-lasting increase in dopaminergic sensitivity. This increase was ascribed to a persistent facilitation of the psychostimulant-induced dopamine outflow from dopaminergic endings in the caudate and nucleus accumbens, or an increased responsiveness of striatal dopaminergic receptors (30,34). There is some evidence showing that at the behavioural, and possibly neural levels, exposure to solvents is able to produce effects similar to those mentioned above. In a series of experiments, von Euler et al. have shown that in

rats tested 16–18 days after a four-week (6 h/day, 5 days/week) low-level (80 ppm) inhalation exposure to toluene, the locomotor response to apomorphine, a direct dopaminergic agonist, was markedly increased (59,60). This result may be regarded as an example of cross-sensitization and the repeated low-level solvent exposure as the sensitizing agent. Of special significance is the fact that it was produced by a concentration of toluene close to the TLV-TWA value recommended for this hydrocarbon (1). An effect similar to that of toluene was also observed in rats treated with 3 ethanol in drinking water for 8 weeks; in these rats the amphetamine-induced locomotor hyperactivity was significantly higher than in the control animals (37). It seems likely that effects similar to those mentioned above may be also produced by exposure to other solvents. Some time ago we studied the long-term behavioural effects of an inhalation exposure to trimethylbenzene isomers: pseudocumene (1,2,4-trimethylbenzene) or hemimellitene (1,2,3-trimethylbenzene) each at the concentration of 0, 25, 100 or 250 ppm. Exposure duration conditions were the same as in von Euler's (59,60) experiments on toluene (6 h/day, 5 days/week for 4 weeks). The behavioural testing started on day 14 and continued till day 60 after the last exposure. It included assessment of short term spatial memory in the radial maze, open-field behaviour, passive and active avoidance learning and hot-plate behaviour. Differences between the exposed and nonexposed rats were found in all test situations except for the radial maze. The exposed rats were slightly hyperactive in the open field, performed worse in the passive and active avoidance situation, and showed stronger and more persistent footshock-induced emotional response. Generally speaking, the results suggest that a decreased ability to inhibit locomotor response in stress-inducing environmental context might constitute the primary cause of the observed behavioural disturbances in the exposed rats (19,61). It has been demonstrated in several studies that a repeated administration of amphetamine or other dopaminergic system-activating drugs sensitizes animals to behavioural effects of footshock i.e. they show an exaggerated locomotor response to this stimulus (4,20,21,29,30,53). The character of behavioural alterations seen in our rats suggests that we were dealing with the same phenomenon; sensitization to the footshock stress, which, in our case, resulted from repeated exposure to trimethylbenzene.

As mentioned above, the neuronal adaptations subserving sensitization induced by psychostimulants are ascribed to some persisting changes in the functional state of the dopaminergic system. The available literature data show that long-term, if not permanent, changes within this system may also develop as a consequence of solvent exposure. The results of von Euler's studies on the binding parameters of the dopamine agonists, suggest that a four-week exposure to toluene at 80 ppm results in a persistent increase in the number of dopamine D2 receptors in the rat neostriatum (60). In another study (23), rats were exposed to toluene (40–320 ppm; 4 weeks, 6 h/day, 5 days/week) and tested after a postexposure period of 29–40 days. The obtained results suggest that exposure to toluene at 80 ppm or less leads to persistent increase in the affinity of dopamine D2 agonist binding in the rat caudate-putamen. Interestingly, no similar changes were observed in rats exposed to xylene or styrene. An increase in dopamine (and other biogenic amine) concentration was found in the hypothalamus, midbrain and medulla oblongata of mice after a 28-day exposure to toluene or benzene in drinking water (25,26). Changes in dopaminergic system which may be related to solvent exposure were

Table 1. Some literature data concerning effects of solvent exposure on the brain catecholaminergic systems

Solvent	Subjects	Administration route, solvent dose/concentration, and exposure duration	Time of testing	Effect	Reference number
Toluene	Rat	Inhalation, 0.7 vol% in the inhaled air, 15 min/day once or for 14 days	Right after exposure	Single exposure: no change in the brain DA and NA levels. Repeated exposure: a significant increase in DA but no change in NA level.	64
Toluene	Rat	Inhalation, 500–1000 ppm, 6 h/day, 5 days/week for 4 weeks	The day after last exposure	Increased DA and NA turnover within various parts of the hypothalamus	2
Toluene	Rat	Inhalation, 0, 100, 300, or 1000 ppm for 8 h	Right after exposure	A significant increase in the whole brain concentration of DA in rats exposed to 100 ppm. In rats exposed to 1000 ppm a significant increase in DA in the striatum, a significant increase in NE in medulla and midbrain.	46
Toluene	Rat	Inhalation, 80–3000 ppm, 6 h/day, 5 days/week for 4 weeks	The day following exposure	A dose-related down-regulation of the DA D2 receptors in the striatum suggestive of a higher transmitter concentration	14
Toluene, xylene, styrene, ethylbenzene, vinyltoluene, 7-methylstyrene	Rabbit	Inhalation, 750 ppm, 12 h/day for 7 days	Right after last exposure	Styrene, vinyltoluene and ethylbenzene caused a marked depletion of striatal and tuberoinfundibular DA and increased homovanillic acid concentration in the same areas	43
Toluene	Rat	Inhalation, 80 ppm, 6 h/day for 4–5 days	2 h after last exposure	Increased DA utilization in the anteromedial frontal cortex and paraventricular hypothalamic nuclei. Increased NA utilization in the paraventricular hypothalamic nuclei	58
Benzene	Mouse	<i>Per os</i> (drinking fluid), 0, 166 mg/l for 28 days.	The day following exposure	Increased level of NE in the hypothalamus, cortex and medulla oblongata. Increased level of DA in the hypothalamus and corpus striatum.	25
Toluene	Mouse	<i>Per os</i> (drinking fluid), 0, 17, 80, 405 mg/l for 28 days.	The day following exposure	Increased levels of biogenic amines and their metabolites in discrete brain regions. The changes were most evident in the 80 mg/l group.	26

Toluene	Rat	Inhalation: 500, 1000 or 2000 ppm for 2 h	During exposure	55
Phenylglyoxylic acid (a styrene metabolite)	Rat	Per os (drinking water), 0, 1250, 3750 or 5000 mg/l for 90 days	The day following exposure	35
Toluene	Rat	I.p. 600-1200 mg/kg, once	Right after exposure	47
Ethanol	Rat	Per os, 5 and 10% vol drinking fluid for 90 days	24 h or 5 days after exposure	48
Ethanol	Rat	Intagastric, 1 g/kg, once daily for 15 days	3 weeks post-treatment	44
Toluene	Rat	Inhalation, 80 ppm, 6 h/day, 5 days/week for 4 weeks	Not before post-exposure day 14	59, 60
Toluene	Rat	Inhalation, 40-320 ppm, 6 h/day, 5 days/week for 4 weeks	29-40 days after exposure	23
Toluene	Humans (volunteers)	Inhalation, 100 ppm for 15 min	PET after exposure	15
Solvent mixtures	Humans (patients)	Occupational exposure for 22 ± 8 years	While in clinic	16

NA - noradrenaline; DA - dopamine; PET - positron emission tomography

also found in humans. In a recent paper, Edling et al. (16) have presented results (of studies with the use of positron emission tomography) suggestive of an increased dopamine synthesis in brains of patients with neuropsychiatric symptoms due to occupational solvent exposure. According to the authors, long-term exposure to organic solvents may increase the rate of dopamine synthesis in the brain without affecting the number of presynaptic terminals or postsynaptic dopamine receptors.

Of importance is the fact that in the Hillefors-Berglund et al. studies, the concentration-effect relationship was nonlinear; of several concentrations of toluene tested, the highest appeared less effective in inducing the increase in the extracellular dopamine than the lower ones (23). A similar nonlinearity was also found in our behavioural studies on trimethylbenzene mentioned above (19); for both (pseudocumene or hemimellitene) isomers the behavioural alterations detected after exposure to 250 ppm were considerably less evident than those found after exposure to 100 (pseudocumene) or even 25 ppm (hemimellitene). The above might suggest that at higher exposure levels, another counterbalancing process, which is leading to persistent changes in the dopaminergic system and behavioural alterations, is also being activated. As a result, the net effect of a high-level exposure is less evident than that observed at lower exposure levels.

To sum up, the above data seem to support the conjecture that exposure to organic solvents, or at least some of them, may initiate TDS, a process which makes the subject hypersensitive to pharmacological and environmental stressors. Like in the case of psychostimulants, this effect is likely to be somehow related to persistent changes in the functional state of the dopaminergic system. Of special importance is the fact that changes within the dopaminergic system and behavioural alterations were found after exposure to solvents at concentrations approaching those recommended for occupational exposure and that the concentration-effect relationship was nonlinear; low concentrations appeared more efficient than the highest ones in producing changes in the dopaminergic system (23) as well as in behaviour (19,61). Bell has noted that, in some cases sensitization occurs when the substance is administered at low doses. High doses do not induce sensitization and even may reverse the process induced by exposure to low doses (7). The efficiency of low-level solvent exposure in inducing persistent behavioural and neurochemical changes, as well as the nonlinearity in the concentration-effect relationship may pose serious problems for those involved in setting occupational and environmental standards of exposure. Therefore, more data on the presumed sensitizing properties of solvents are urgently needed.

As suggested by Antelman et al. (6), the most important factor in triggering TDS by a chemical is its foreignness and stressfulness to the organism rather than any specific pharmacological property. A solvent, like many other substances assessed experimentally for neurotoxicity, is almost always foreign and always stressful (due to its odour) for the experimental subjects (usually rats), and as such, it should be able to trigger TDS. It is not quite certain, however, that pharmacological properties of the substance under study do not matter. For example, sensitization by repeated treatment with methamphetamine appear to be preventable by scopolamine or clonazepam, and, neither scopolamine, nor clonazepam produced sensitization when given alone (27,45). The above contradicts Antelman's suggestion and shows that pharmacological properties of a substance may consist important factors in

triggering the sensitization process and, possibly, determining its behavioural outcome. As far as organic solvents are concerned, any data from a study aimed at detecting and comparing the sensitizing properties of different solvents have not yet been published. The results obtained by von Euler et al. (59,60) show that such properties characterize toluene. However, in experiments carried out by Hillefors-Berglund et al., changes in the dopaminergic system similar to those produced by exposure to toluene, were not observed after exposure to xylene or styrene which may suggest that the latter two solvents differ from toluene in the sensitization potential (23). It should be established therefore, in specially designed studies, whether exposure to other common organic solvents can sensitize the exposed subjects to these solvents and to other chemical or physical stressors. Data obtained in these studies might be of help in assessing the risk of sensitization induction, and by the same of MCS, associated with exposure to a given solvent.

REFERENCES

1. American Conference of Governmental Industrial Hygienists, Threshold Limit Values for Chemical Substances and Physical Agents. Biological Exposure Indices, 1999.
2. Andersson K, Nilsen OG, Toftgard R et al. Increased amine turnover in several hypothalamic noradrenaline terminal systems and changes in GH, LH and prolactin secretion in the male rat by low concentrations of toluene. *Neurotoxicology* 4: 43–51, 1983.
3. Antelman SM. Stressor-induced sensitization to subsequent stress: implications for the development and treatment of clinical disorders. In: *Sensitization in the Nervous System*. Eds. PW Kalivas, CD Barnes. Telford Press, Caldwell, New York, 1988.
4. Antelman SM, Eichler AJ, Black CA, Kocan D. Interchangeability of stress and amphetamine in sensitization. *Science* 207: 329–331, 1980.
5. Antelman SM. Time-dependent sensitization in animals: a possible model of multiple chemical sensitivity in humans. *Toxicol Ind Health* 10: 335–342, 1994.
6. Antelman SM, Soares JC, Gershon S. Time-dependent sensitization - possible implications for clinical pharmacology. *Behav Pharmacol* 8: 505–514, 1997.
7. Bell IR. Clinically relevant EEG studies and psychophysiological findings: possible neural mechanisms for multiple chemical sensitivity. *Toxicology* 111: 101–117, 1996.
8. Bell IR, Schwartz GE, Amend D, Peterson JM, Stini WA. Sensitization to early life stress and response to chemical odors in older adults. *Biol Psychiatry* 35: 857–863, 1994.
9. Bell IR, Schwartz GE, Baldwin CM et al. Individual differences in neural sensitization and the role of context in illness from low-level environmental chemical exposure. *Environ Health Perspectives* 105: 457–466, 1997.
10. Bolla KI, Roca R. Neuropsychiatric sequelae of occupational exposure to neurotoxins. In: *Occupational Neurology and Clinical Neurotoxicology*. Eds. M Blecker, JA Hansen. Williams and Wilkins, Baltimore, 1994.
11. Böck KW, Birbaumer N, MCS (Multiple Chemical Sensitivity): Cooperation between toxicology and psychology may facilitate solutions of the problems: commentary. *Hum Exp Toxicol* 16: 481–484, 1997.
12. Bowen SE, Balster RL. Effects of inhaled 1,1,1-trichloroethane on locomotor activity in mice. *Neurotoxicol Teratol* 18: 77–81, 1996.
13. Cador M, Bijiou Y, Stinus L. Evidence of a complete independence of the neurobiological substrates for the induction and expression of behavioural sensitization to amphetamine. *Neuroscience* 65: 385–395, 1995.
14. Celani MF, Fuxe K, Andersson K, Hansson T et al. Effects of subacute treatment with toluene on central monoamine receptors in the rat. Reduced affinity in [3H]5-hydroxytryptamine binding sites and in [3H]spiperone binding sites linked to dopamine receptors. *Toxicol Lett* 17: 275–281, 1983.

15. Edling Ch, Hellman B, Arvidson B et al. Positron emission tomography studies of healthy volunteers: no effects on the dopamine terminals and synthesis after short-term exposure to toluene. *Exp Toxicol* 16: 171–176, 1997.
16. Edling Ch, Hellman B, Arvidson B et al. Do organic solvents induce changes in the dopaminergic system? Positron emission tomography studies of occupationally exposed subjects. *Int Arch Occup Environ Health* 70: 180–186, 1997.
17. Evans EB, Balster RL. CNS depressant effects of volatile organic solvents. *Neurosci Biobehav Rev* 15: 233–241, 1991.
18. Glowa JR. Comparisons of some behavioral effects of d-amphetamine and toluene. *Neurotoxicology* 8: 237–248, 1987.
19. Gralewicz S, Wiaderna D, Tomas T, Rydzynski K. Behavioral changes following a four-week inhalation exposure to pseudocumene (1,2,4-trimethylbenzene) in the rat. *Neurotoxicol Teratol* 19: 327–333, 1997.
20. Hammamura T, Fibiger HC. Enhanced stress-induced dopamine release in the prefrontal cortex of amphetamine-sensitized rats. *Eur J Pharmacol* 237: 65–71, 1993.
21. Hammamura T, Ichimaru Y, Fibiger HC. Amphetamine sensitization enhances regional c-fos expression produced by conditioned fear. *Neuroscience* 76: 1097–1103, 1997.
22. Herman JP, Stinus L, le Moal M. Repeated stress increases locomotor response to amphetamine. *Psychopharmacology* 84: 431–435, 1984.
23. Hillefors-Berglund M, Liu Y, von Euler G. Persistent, specific and dose-dependent effects of toluene exposure on dopamine D2 agonist binding in the rat caudate-putamen. *Toxicology* 100: 185–194, 1995.
24. Hinman DJ. Biphasic dose-response relationship for effects of toluene inhalation on locomotor activity. *Pharmacol Biochem Behav* 26: 65–69, 1987.
25. Hsieh GC, Sharma RP, Parker RD. Subclinical effects of groundwater contaminants. IV. Effects of repeated oral exposure to combination of benzene and toluene on regional brain monoamine. *Arch Toxicol* 64: 669–676, 1990.
26. Hsieh GC, Sharma RP, Parker RD, Coulombe RA Jr. Evaluation of toluene exposure via drinking water on levels of regional brain biogenic monoamines and their metabolites in CD-1 mice. *Ecotoxicol Environ Saf* 20: 175–184, 1990.
27. Ito K, Ohmori T, Abekawa T, Koyama. Clonazepam prevents the development of sensitization to methamphetamine. *Pharmacol Biochem Behav* 810: 875–879, 1997.
28. Jones SR, Gainetdinov RR, Wightman RM, Caron MG. Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. *J Neurosci* 18: 1979–1986, 1998.
29. Kalivas PW, Richardson-Carlson R, Van Orden G. Cross-sensitization between foot shock stress and enkephalin-induced motor activity. *Biol Psychiat* 21: 939–950, 1986.
30. Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Res Rev* 16: 223–244, 1991.
31. Kelly PH, Iversen SD. Selective 6-OHDA-induced destruction of mesolimbic dopamine neurons: Abolition of psychostimulant-induced locomotor activity in rats. *Eur J Pharmacol* 40: 45–56, 1976.
32. Kiriu T, Ameno K, Fuke C et al. The distribution of toluene in the brain and its effects on the brain catecholamines in acute toluene poisoning. *Nippon Hoigaku Zasshi* 44: 25–33, 1990.
33. Kondo H, Huang J, Ichihara G et al. Toluene induces behavioral activation without affecting striatal dopamine metabolism in the rat: behavioral and microdialysis studies. *Pharmacol Biochem Behav* 51: 97–101, 1995.
34. Kuczenski R, Segal DS. Sensitization of amphetamine-induced stereotyped behaviors during the acute response: role of D1 and D2 dopamine receptors. *Brain Res* 822: 164–174, 1999.
35. Ladefoged O, Lam HR, Ostergaard G et al. Toxicity of the styrene metabolite, phenylglyoxylic acid, in rats after three months' oral dosing. *Neurotoxicology* 19: 721–737, 1998.
36. Lanier LP, Isaacson RL. Early developmental changes in the locomotor response to amphetamine and their relation to hippocampal function. *Brain Res* 126: 567–575, 1977.
37. Lograno DE, Matteo F, Trabuchi M et al. Effects of chronic ethanol intake at low dose on the rat dopaminergic system. *Alcohol* 10: 45–49, 1993.

38. Meggs WJ, Dunn KA, Bloch RM, Goodman PE, Davidoff AL. Prevalence and nature of allergy and chemical sensitivity in a general population. *Arch Environ Health* 51: 275–282, 1996.
39. Mikkelsen S. Epidemiologic update on solvent neurotoxicity. *Environ Res* 73: 101–112, 1997.
40. Miller CS, Mittel HC. Chemical sensitivity attributed to pesticide exposure versus remelling. *Arch Toxicol Ind Health* 19: 369–386, 1994.
53. Sorg BA, Kalivas PW. Effects of cocaine and footshock stress on extracellular dopamine levels in the ventral striatum. *Brain Res* 559: 29–36, 1991.
54. Sorg BA, Prasad BM. Potential role of stress and sensitization in the development and expression of multiple chemical sensitivity. *Environ Health Perspectives* 105: 467–471, 1997.
55. Stengard K, Hoglund G, Ungstedt U. Extracellular dopamine levels within the striatum increase during inhalation exposure to toluene: a microdialysis study in awake, freely moving rats. *Toxicol Lett* 71: 245–255, 1994.
56. Stollery B. Organic solvents. In: *Handbook of Human Performance*. Vol. 1. The Physical Environment. Eds. AP Smith, DM Jones. Academic Press, London, 1992.
57. Vezina P. D1 dopamine receptor activation is necessary for the induction of sensitization by amphetamine in the ventral tegmental area. *J Neurosci* 16: 2411–2420, 1996.
58. von Euler G, Fuxe K, Hansson T et al. Effects of acute haloperidol treatment on regional catecholamine levels and utilization in rats exposed to toluene. *Acta Physiol Scand* 132: 199–208, 1988.
59. von Euler G, Ogren S-O, Li XM, Fuxe K, Gustafsson JA. Persistent effects of subchronic toluene exposure on spatial learning and memory, dopamine-mediated locomotor activity and dopamine D2 agonist binding in the rat. *Toxicology* 77: 223–232, 1993.
60. von Euler G, Ogren SO, Li XM, Fuxe K, Gustafsson JA. Persistent effects of 80 ppm toluene on dopamine-regulated locomotor activity and prolactin secretion in the male rat. *Neurotoxicology* 15: 621–624, 1994.
61. Wiaderna D, Gralewicz S, Tomas T. Behavioural changes following 4-week inhalation exposure to hemimellitene (1,2,3-trimethylbenzene) in the rat. *Int J Occup Med Environ Health* 11: 319–334, 1998.
62. Wood RW. Stimulus properties of inhaled substances. *Environ Health Perspect* 26: 69–76, 1978.
63. Wood RW, Colotla VA. Biphasic changes in mouse motor activity during exposure to toluene. *Fundam. Appl Toxicol* 14: 6–14, 1990.
64. Yamawaki S, Sarai K. Effects of toluene inhalation on locomotor activity and brain catecholamine levels in rats. *Yakubutsu Seishin Kodo* 2: 57–59, 1982.

Received for publication: August 4, 1999

Approved for publication: November 16, 1999

