

Implications For Cognitive Rehabilitation and Brain Injury From Exposure to Methyl Ethyl Ketone (MEK): A Review

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Methyl ethyl ketone (MEK) is an organic solvent used extensively in the print and paint industry. It is one of many applications but is very commonly used either on its own or in combination with other solvents. In the United States (US), production of MEK exceeds \$1.5 million annually. The US Environmental Protection Agency has listed it as a hazardous chemical; various reports state physical, psychological and neuropathic effects at specific levels of exposure of MEK. Consequentially, poor health of workers creates an economic problem for the industry, and with claims for compensation increasing, this situation means that there is an urgent need to address the problem so that litigation may be pursued quickly to benefit victims.

Neuropsychological assessment is an essential part of establishing probabilistic evidence of causation of effect following exposure to MEK. Approaches that originate from both Neuroscience and Psychology contribute significantly to the ongoing legislative process and to treatment prospects for victims. Specific recommendations for incorporating tests within the neuropsychological battery of assessment tests is presented and discussed

in detail to enable examiners to properly assess clients who have been exposed to MEK. This will help clinicians and assessors provide appropriate cognitive rehabilitation as well as to support compensation claims.

INTRODUCTION

Methyl ethyl ketone (C₄H₈O) or MEK (CEPA, 1999) (Figures 1 & 2, Wikipedia, 2009) is a colourless liquid that has a sweet or sharp, and fragrant acetone-like odour. It has also been described as minty, and with an irritating and unpleasant odour; and an odour threshold (at which it may be detected) of about 16 parts per million (ppm) (García, 2008). MEK is also known as 2-butanone (USEPA, 1999), methyl acetone, ethyl methyl ketone, and methyl propanone.

The vapour of MEK is heavier than air, soluble in water, ether, acetone and benzene, and is extremely flammable. It can form explosive mixtures with oxygen (or air) concentrations of between 1.4 per cent and 11.4 per cent. It is particularly hazardous because it can spread long distances and therefore, it has the possibility of distant ignition and also flashback (García, 2008).

MEK is a naturally occurring molecule in volcanoes, and in forest and bush fires. It also occurs in some foods. It is present in products that are subject to biological degradation and in motor vehicle exhaust. MEK is predominantly used in the manufacture of paints, paint removers, varnishes and lacquers, glues and resins, rubbers, plastics, cellulose acetate and nitrocellulose, and in artificial leather. It

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is used in the printing industry, and as household hard surface cleaners in liquid and aerosol forms, and in dyes and waterproofing compounds (OSH, 2009).

In the US, it is produced in high volume with annual production exceeding \$1.5 million (OSH, 2009). The United States National Aeronautical & Space Administration (NASA) maintains an active interest in the environmental conditions associated with living and working in spacecraft. Identifying hazards that might adversely affect the health (and well-being) of crew members, is a part of this interest. Following thorough investigation by the Board on Environmental Studies and Toxicology (BEST), spacecraft water exposure guidelines (SWEGs) have been developed for several chemicals including MEK (García, 2008). Therefore, this compound is highly significant and important in terms of its contribution and potential impact upon our increasing cognitive rehabilitation patient population.

Physical effects of exposure

The amount of solvent for which there is no adverse medical effects expected is termed 'The Threshold Limit Value' or TLV. For an 8 hour exposure to MEK, the TLV is 200 ppm (or about 590 mg/cum of air), and the recommended short-term exposure limit is 15-minutes for 300 ppm. However, the TLV is derived from acute, high-level exposure incidents, and not to long-term, low-level exposures (Pactox, 2009).

MEK is absorbed quickly through the lungs upon inhalation of the vapour. The steady-state concentration in expired air after breathing MEK vapours is about 30% of environmental concentration (Perbellini, Brugnone, Mozzo, Cocheo & Caretta, 1984). This indicates an overall alveolar retention of about 70 per cent.

Additionally, MEK may be absorbed quickly through intact skin. Several decades ago, Munies and Wurster (1965) reported that the application of MEK to the skin of one forearm leads to levels of MEK in expired air equivalent to breathing in the lungs at least 10 ppm. Furthermore, contact of the solvent with a larger skin area is likely to be proportionally

equivalent to more absorption which, theoretically, would exceed the absorption of the vapour through the lungs and therefore, increasing the overall exposure of the individual to MEK.

The effect of acute exposure to MEK depends upon the extent and also the duration of exposure. MEK is an irritant of the mucous membrane and upper airway which produces slight nose and throat irritation at about 100 ppm. However, strong irritating effects occur also at 350 ppm (OSH, 2009; USEPA, 1987).

In a study reported by the Canadian Center for Occupational Health and Safety (CCOHS, 2009), 143 volunteers exposed to 220 ppm for 4 hours, reported throat irritation, unpleasant odour, nausea, and headache.

Cytogenic damage has also been seen following occupational exposure to organic solvents including MEK, using exfoliated buccal cells samples (Burgaz, Erdem, Cakmak, Erdem, Karakaya & Karakaya, 2002). This type of tissue sampling is now an established and appropriate way of measuring exposure to such organic solvents. Chemical analysis of urine also helps to determine exposure levels to MEK (USEPA, 1990).

This is particularly important for detecting the urinary metabolite of MEK, acetylmethylcarbinol (also known as 3-hydroxy-2-butanone or AMC). However, this has limited use as a measurement as it accounts for about 0.1 per cent of the total urinary excretion of MEK and AMC of an absorbed dose (Perbellini, Brugnone, Mozzo, Cocheo & Caretta, 1984).

Levels of MEK in urine greater than 0.8 ppm have been associated with airborne concentrations of about 30 ppm, and those urinary concentrations of above 1.0 ppm are associated with airborne concentrations above 50 ppm (Miyasaka, Kumai, Koizumi, Watanabe, Kurasako, Sato & Ikeda, 1982).

This has led others (Lauwerys, 1983) to propose a maximum permissible value of 2.6 mg of MEK in urine per gram of creatinine. This amount of creatinine in the urine corresponds to an exposure level of about 200 ppm of MEK.

Psychological and neurological effects of exposure

The problems associated with occupational exposure to MEK appear to be truly global. For example, workers in Romania exposed to MEK suffered from mood disorders, irritability, memory difficulties, sleep disorders, and headaches (Mitran, Callender, Ohra, Dragnea & Botezatu, 1997). Complex behavioural disturbances have indicated an underlying neurotoxic syndrome which was revealed by neuropsychological testing. Indeed, MEK was found to be the most neurotoxic of the three ketones that were systematically tested.

Rehabilitation of patients with memory difficulties is often labour-intensive and protracted. It is very frustrating for the patient because simple task instructions may not even be understood or processed if the impairment of functioning involves working memory (Thompson, 2006).

Several studies have suggested that MEK can increase the neurotoxic effects of other solvents. For example, the neurotoxic effects of methyl n-butyl ketone and n-hexane can be increased and causes a neuropathy that is typically a symmetrical distal sensory and motor neuropathy and without loss of deep tendon reflexes, initially (NIOSH, 1978). The syndrome is often irreversible. However, it does not appear that MEK alone causes such a neuropathy although it can still contribute directly to impaired memory functioning. This also means that workers need to be vigilant in the range of chemicals they use if MEK is to be used in the same environment as others with potential indirect effects.

NEUROPSYCHOLOGICAL ASSESMENT

Approaches used in neuroscience and psychology are useful in addressing the problem that growing numbers of workers are filing for compensation because of exposure to occupational levels of solvents across the world. In the United Kingdom (UK), there have been litigation suits for workers being exposed to organophosphates (for example “sheep dip”), particularly, in agriculture employment.

There are similar problems with assessing such people who have been exposed to these chemicals;

and neuropsychology has been highly productive in providing a functional profile of neuropsychological deficits arising from occupational exposure, especially in respect of the long-term use and exposure.

It has been recognised (for example, Morris, 1999) that occupational solvents can give rise to neuropathy and impaired cognitive functioning that may be usefully assessed by the neuropsychological assessment. However, to date, clear and concise information of neuropsychological tests to be used and the measures they make, have not been well-documented.

The application of the neuropsychological assessment has been recognised in making diagnosis and prognosis of other conditions that compromise health such as human immunodeficiency virus (HIV) (Thompson, 1998). Particularly, in claims for compensation, techniques borrowed from neuroscience and neuropsychology have been useful in deciding who is genuine and who is not (Thompson, 2003), especially since neuroscience facts cannot lie even if they are found to have been masked by some other effects.

Neuropsychological testing

As with suspected neuropathy and impaired cognitive functioning, it is advisable to administer a series of neuropsychological tests to determine the nature and extent of deficit. The battery of tests can provide a profile of the functional abilities of the client which can also highlight specific deficits in functioning for further investigation and corroboration. The following tests are recommended and explained more fully in order to assist the clinician in helping the patient during cognitive rehabilitation or for the purposes of compensation litigation procedure:

1. General and Personal Orientation
2. Wechsler Adult Intelligence Scale (WAIS)
3. National Adult Reading Test (NART)
4. Benton Visual Retention Test (BVRT)
5. Wechsler Logical Memory sub-scale (WMS)
6. Trail Making Test (TMT)

7. Rey-Osterreith Complex Figure Test (ROCT)
8. Star Cancellation Task and Single Letter Cancellation Task (SLCT)
9. Controlled Oral Word Association Test (COWAT)
10. Paired Associates Test (PAT)
11. Hospital Anxiety and Depression Scale (HADS)

1. General and Personal Orientation

When testing any individual, it is advisable to check if there is any particular reason why they should not be able to provide their personal details such as where they live, their name and age, and their occupation. There are many useful checklists available (Thompson, 1993) for this purpose. In addition, it is useful to check if they are correctly orientated to the day when being tested, the name of the Prime Minister (or Governor/President) of the country and the month and year of testing. There are various formats for this type of testing but often it is easier to tailor this to the particular client being tested and arrive at an overall score for quick reference. There are no norms for such a test but it is useful to know if the client's responses are typical or uncharacteristic when corroborated with a spouse, close friend or work colleague.

2. Wechsler Adult Intelligence Scale (WAIS)

This is a well-known test that has been revised several times (Wechsler, 1981). The latest version is Version IV. The WAIS comprises several sub-tests that each tap into a particular function or ability. For MEK exposure, it is important to determine whether or not the client has been affected in terms of any of their usual abilities and therefore, the WAIS is able to provide an overall cognitive profile of the client's functional abilities. There is a shortened version of the WAIS which still has validity and is recognised by the UK Courts for Expert Witness presentation. The sub-tests of the shortened version can be listed as follows together with their measurement aims:

a) Information

This sub-test taps the individual's general knowledge, and individuals who do well usually are alert to the environment and have good long-term memory for facts. Scores reflect the client's education and therefore, are not generally affected by the effects of exposure to MEK.

b) Digit Span

This sub-test measures short-term auditory memory for number sequences but also reflects attention span and the individual's ability to concentrate. Deficits on this sub-test may show that processes involved in attending to information to be remembered (and then retrieved) are impaired. Hence, this score may be sensitive to the effects of MEK exposure.

c) Arithmetic

This sub-test of the WAIS requires the individual to solve numerical problems without the aid of a pencil and paper. There are no unusual skills required, only the application of basic arithmetic functions to solve problems presented aurally. Scoring well on this sub-test may reflect education and occupationally learned ability; however, as with head injury, often clients experience competing and interfering processes because of brain damage resultant of their exposure to MEK or to exposure to organo-solvents (or solvent abuse).

d) Comprehension

This sub-test attempts to measure "common sense reasoning" and the ability to make social judgement in practical situations. It also assesses the individual's exposure to mainstream culture. Therefore, it is generally unaffected by the effects of exposure to compounds unless they interfere directly with perceptual processes such as hallucinatory

substances. It is not generally believed that MEK has such hallucinatory characteristics.

e) Similarities

The ability to see relationships between things and ideas, and to categorise them into logical groups is assessed by this sub-test. It also measures the capacity to form “conceptual units” from verbal material and to express them in words. Where language ability is affected due to the effects of exposure to compounds, sometimes performance on this sub-test is effected. However, it is unlikely that this sub-test should be affected by exposure to MEK.

f) Picture Completion

This sub-test measures the individual's alertness to visual detail and also the ability to understand meaning and details within a complete picture. Visual memory is also reflected in the performance on this sub-test. Hence, this process may be affected by exposure to MEK which can affect the ability to remember items.

g) Picture Arrangement

This sub-test requires the individual to evaluate the social relevance of pictured situations. It also requires an ability to anticipate the consequences of actions, and to distinguish “essential” from “irrelevant” details. This sub-test is sometimes considered a measure of planning ability which is usually regarded to be the responsibility, to some extent, of the frontal lobes of the brain. Performance on this sub-test is often affected by the effects of exposure to solvents such as MEK.

h) Block Design

This is a measure of the ability to analyse abstract figures visually and then to construct them from their component parts. It is

essentially a measure of ability to handle “spatial” relations. Again, unless perceptual abilities are affected directly then the effects of MEK exposure are unlikely to be altering significantly performance scores on this sub-test.

i) Digit Symbol

This sub-test measures visuo-motor speed and scores may be affected by visual memory, co-ordination, and the ability to learn non-verbal material. Since there is a requirement of good visual memory ability, then solvent exposure is expected to affect performance on this sub-test.

Although there are other sub-tests contained within the WAIS, the shortened version, prorated for those sub-tests not administered, is a fairly accurate, robust and valid test on the testing battery. It is also recognised in UK Courts as submissible as part of the Expert Witness testimony.

Three scores are achieved from using these sub-tests: (1) verbal intelligence quotient (IQ); (2) performance IQ; and (3) full-scale IQ.

3. National Adult Reading Test (NART)

This test provides the examiner with an estimate of the pre-morbid IQ of the patient (Nelson, 1991) based on verbally mediated components. Unless language has been affected by previous trauma, this test can be used and compared with the WAIS so that a judgement can be made, based on the normative population, of current versus pre-morbid IQ levels. The effects of exposure to MEK may impact on the patient's functional abilities sufficiently to affect a depression of performance scores on the WAIS. Hence, there may be a significant difference between current and pre-morbid full-scale IQ.

4. Benton Visual Retention Test (BVRT)

This test assesses the patient's ability to remember visually-presented stimuli (Benton Sivan, 1991). Performance scores are divided into correct scores and error scores where the latter are categorised into particular errors such as omissions, substitutions of stimuli, misrepresentations, size errors and spatial errors. There are parallel versions available for re-testing of patients over time periods and computerised versions are also available (Thompson, Ennis, Coffin & Farman, 2007). Effects of solvents on visual memory and spatial ability may be demonstrated by testing, and there are well validated normative groups available for comparison aged 30 years and above. The author is currently collecting and validating data in the specific age group 18-35 years to complete the across-range norms.

5. Wechsler Logical Memory sub-test (WMS)

This sub-test of the WMS (Wechsler, 1988) is particularly useful as a test of auditory verbal memory that may be affected by MEK exposure. It assesses a patient's ability to memorise simple instructions and to retrieve and recall information. There is a delay element to the test enabling the patient to be tested again after a 30-minute delay to determine if recall is also affected by time span.

6. Trial Making Test (TMT)

This is a test of reaction time as well as information processing capacity and arose from the construction of the Army Individual Test of General Ability (Reitan, 1958). Later revisions of the test (Corrigan & Hinkeldey, 1987; Gaudino, Geisler, & Squires, 1995) allow for assessing the patient's ability to follow a sequence of numbers (Part A) and a sequence of letters and numbers (Part B) as quickly as possible. Timed performances may be affected by an inability to concentrate, or by competing processes and dysfunctional thought processes involved in carrying out the task. MEK exposure may affect the patient's ability to concentrate and follow the rules that are well learned.

7. Rey-Osterreith Complex Figure Test (ROCT)

The ROCT is useful to establish whether or not visual memory and visual spatial ability has been affected (Osterreith, 1944; Rey, 1941). Number of errors made during the reproduction of a complex drawing signifies the patient's deficits that may have arisen from memory re-processing dysfunction or visual spatial disability. There is also a delay element where the patient's recall ability is assessed. Parallel versions are available for re-testing.

8. Star Cancellation Task and Single Letter Cancellation Task (SLCT)

The SLCT (Zoccolotti, Antonucci, Judica, Montenero, Pizzamiglio & Razzano, 1989) assesses the patient's spatial awareness and is particularly sensitive to visual hemianopia whose origin is in stroke. It is less likely to be affected by MEK exposure but is a ready check on visual field deficits that may impact on performance on other tests and therefore, helps excluded other confounding dysfunctions.

9. Controlled Oral Word Association Test (COWAT)

It is not usual for MEK exposure to affect language and verbal fluency; however, using the COWAT (Ardila, Ostrosky-Solis & Bernal, 2006; Lezak, 1995; Loonstra, Tarlow & Sellers, 2001) completes the patient's profile of functional abilities and tends to corroborate findings obtained on other tests such as the NART.

10. Paired Associates Test (PAT)

This is a very useful test because it allows the examiner to assess the patient's ability to learn new information, both abstract and concrete. Derived as far back as 1894 by Mary Whiton Calkins (Calkins, 1894), it requires the client to learn a series of word-pairs such as 'metal-iron' or 'school-grocery' over three trials. The pairing consists of 'hard' (concept) word-pairs as well as 'easy' (logical) word-pairs. The

patient has to provide the missing word in the pair when the examiner issues the first word of the pair. It is sensitive to the effects of head injury, solvent abuse and potentially to exposure to compounds such as MEK.

11. Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond & Smaith, 1981) is a well-validated test that is widely used clinically and in research. Scores obtained for levels of anxiety and depression inform the examiner of possible confounding variables acting upon the performance on various neuropsychological tests. There is also suggestion that exposure to certain solvents and solvent abuse leads to clinical depression, though this is subject to further debate.

Advantages of a neuropsychological test battery for MEK exposure

Well known and standardised tests such as the WAIS have the advantage of enabling normative comparison. Throughout experimental psychology, normative comparison is favoured albeit with consideration of case study paradigms (taken from clinical psychology) in order to be mindful of individual differences. In particular, the BVRT (Benton Sivan, 1991; Thompson, Ennis, Coffin & Farman, 2007) can provide evidence of visual memory and visuo-spatial deficits whilst the PAT can provide evidence of difficulties in the ability to learning new information in a trial-by-trial paradigm (Wechsler, 1988).

Although it is important to provide a global profile through testing to show evidence (or the lack of evidence) of deficits (Kapur, Scholey, Moore, Barker, Brice & Thompson, 1996; Thompson & Berry, 1997), it is equally important to thoroughly investigate difficulties in a specific domain. For example, the TMT (Thompson, MacDonald & Coates, 2001) can show difficulties in information processing and reaction time slowness whilst the Wechsler Logical Memory sub-scale (Wechsler, 1988) can show evidence of specific auditory verbal memory problems.

By building up a picture of deficits (and abilities), as well as any evidence of mood dysthymia - assessed using the clinical interview and a mood questionnaire, for example, the HADS (Zigmond & Snaith, 1983) - the neuropsychologist can establish a pattern of normality and abnormality and attribution to known contributors such as exposure to solvent over a prolonged duration. It is this scientific approach that assists neuropsychologists in their presentation of facts in contribution to medico-legal arguments and claims for compensation.

As an Expert Witness, this process is invaluable to deciding the probability of neuropathological effects being caused by alien products in occupational/industrial environments. This is a valuable contribution to the legal process and in turn, to the economy not only because it has the potential of speeding up the legal process but also because it indirectly influences policy change and industrial working efficiency through regulation of hazardous chemicals.

Importantly, correct identification of deficits through MEK exposure will also provide clinicians with information to assist their patients through cognitive rehabilitation. A part of advancing our knowledge of clinical assessment in many fields of medicine and neuropsychology (Thompson, 2010), is being able to provide more direction and help for patients in pin-pointing the specific rehabilitative needs of impaired patients.

CONCLUSIONS

The United States Environmental Protection Agency (EPA) denied the petition submitted by the Ketones Panel of the Chemical Manufacturers Association (CMA) to delete MEK from the Emergency Planning and Community Right-to-Know Act (EPCRA) section 313 list of toxic chemicals compiled by the 1986 Act (Federal Register, 1998a; Goldman, 1998). The grounds were that MEK contributes to the formation of ozone, which causes serious adverse human health and environmental effects at relatively low doses. Previously, the EPA stated in the 61432 Federal Register of 30 November 1994, that ozone meets the listing criteria of the

EPCRA section 313 (d) (2) (B) and (C) (Goldman, 1998).

It is important to note that whether the toxic effects of MEK are caused directly by a one-step process or indirectly by a degradation product of the chemical (or even by a second or subsequent solvents created by or acted on), the toxic effect still occurs as a result of the presence of MEK. Therefore, it makes no difference whether the toxic chemical was a result of chemical reactions. After all, this type of indirect toxicity is similar to nonlinear carcinogens that induce cancer through a “two-step” mechanism.

Knowing the neuropsychological sequelae of exposure to MEK is important so that we can quantify and provide appropriate advice to patients. As these sequelae differ between patients, we need to tailor rehabilitation accordingly to individual patients. However, we have advanced our knowledge in providing a clearer picture of the effects of MEK and therefore are now able to provide a comprehensive neuropsychological test battery to measure potential deficits in a responsible and scientific manner.

The EPA rightly argues that were it to exclude indirect effects from consideration of including certain chemicals in the list, then this would effectively preclude public access to information about substances that may cause adverse health and environmental effects, such as MEK. Further legislation in the US controls the exportation of solvents because of the potential health hazards (Federal Register, 1998b).

Others have attempted to reduce the amount of solvent used in specific applications such as in the painting of vehicles (Elion, Flanagan, Turner, Hanley & Hill, 1996). They showed that the amount of airborne MEK can be significantly reduced during some applications.

However, significant and sufficient data is still required to accurately correlate the ppm quantum with criteria (eg Hill) and performance test data obtained on neuropsychological tests. This is partly because data is often historic and actions required to assess patients (or clients) arise from law suits that are “after the event”. It is difficult to obtain “clean”

matched-controlled data that correlates with neuropsychological test results.

The need for a worldwide pre-manufacture inventory of toxic chemicals that produce health effects classed as Persistent Organic Pollutants (POPs) led to the establishment of the Stockholm Convention on POPs in May 2001. A number of nations signed up to the treaty that includes provisions to include additional POPs and to prevent the introduction of new POPs into commerce.

For adding new chemicals, an international committee of government-appointed scientists will decide whether the required criteria of persistence, bio-accumulation, potential for long-range transport, and also adverse effects to human health (or to the environment) are met; and therefore, whether to recommend adding the chemical to the treaty. Typically, it may take about five years for a chemical to be nominated and ultimately added to the Convention.

Goldman (2006) comments: “This is enough time to involve industry and the public in a deliberate process and to assure that the outcome is not a surprise to anyone.” Although this is perhaps the most reassuring for our future generations, it is also recognition that we have a large problem with the chemicals we use routinely and that there are potential detrimental effects to our health whether used directly or indirectly and even through airborne exposure. The psychological, environmental and economic impact is great. However, we have the knowledge to use neuroscience to inform economic reform and to help victims of occupational negligence.

DECLARATION

This research received no funding from any agency in the public, commercial, or voluntary sectors.

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