Methyl Iodide Public Health Protections for Older Children

Testimony Provided to the Scientific Advisory Board on Methyl Iodide

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Key Points:

I. The exposures of older children to Methyl Iodide (MeI) as a result of their work in agriculture requires careful evaluation. Adolescents (ages 12 to 17) are routinely employed in agricultural work, which creates clear opportunities for exposure. Multiple hazardous situations where health damage can occur are prevalent in agricultural work. In addition, older children have elevated inhalation rates compared to adults, increasing their short term and cumulative exposure levels above those of many other members of the population.

II. Older children undergo intense and rapid brain development and substantial hormonal changes. They are highly susceptible to neurotoxic chemicals and MeI is a neurotoxin. Hormone disruptors also pose specific serious problems for older children, and MeI is a hormone disruptor. There is insufficient scientific information on which to base a claim that a "safe" level of exposure can be determined for older children.

I. Exposure

Those who work in the fields where MeI could be applied are likely to be exposed on a regular basis to MeI. All workers who performing tasks that disturb surface soil will bring MeI contamination to the surface and generate dust contaminated by MeI. Soil ingestion during outdoor work can be substantial (see US EPA Exposure Factors Handbook). Their near ground-level exposures at times, as well as dust generation during agricultural activities can yield intakes many times higher than a typical breathing zone (standing height) concentration.

Inhalation is much greater during manual labor and rates among adolescents doing this kind of work are among the highest, almost 60 m(3) for an 8 hour workshift (EPA Exposure Factors Handbook). Contamination of the 60 out of approximately 70 m(3) inhaled during a 24 hour period means that the proportion of uncontaminated air is small and the dose can be substantial.
As unskilled workers, teens are more likely to engage in labor-type jobs and often have minimal training in worker protection strategies. Thus, it is relevant to consider whether this poses a serious risk to this population subgroup.

II. Susceptibility

Medical studies indicate the adolescent brain has a greater susceptibility to disruption than would be found in an adult. This is directly relevant to Mel, which is a neurotoxin. There are clearly developmental processes continuing into adolescence and the increased sensitivity that this generates has been illustrated in studies of many chemicals. Appendix A contains the abstracts of the studies discussed below.

White and Swartzwelder (2005) report on clear evidence that adolescence represents a unique stage of brain development. Changes in brain organization and function during adolescence are widespread, and include intense rewiring in the frontal lobes and other neocortical regions, as well as changes in a litany of subcortical structures.

Schweinsburg et al (2005) studied changes that occur in the frontal and parietal neural networks involved in spatial working memory over adolescence using functional MRI imaging. These substantial changes occurred as a part of normal brain development.

Walker et al (2004), evaluated adolescent stress sensitivity and vulnerability for the emergence of the mental disorders. They identified hormonal changes as a key element in expression of genetic vulnerabilities for psychopathology. They found both activational and organization effects of hormones on the adolescent brain that contribute to developmental discontinuities in behavioral adjustment with implications for adult psychopathology.

Saddik et al (2005) studied the effects of solvent exposure on memory and motor dexterity in male working children ages 10 to 17. They found an association between exposure to solvents and neurobehavioral performance on a number of non-computerized tests for working children exposed to solvents in comparison with nonexposed working children and nonexposed children at school. Performance on memory tests and motor dexterity were reduced and mood tests indicated more anger and confusion than among the unexposed working or nonworking children.

Abreu-Villaca et al (2004) studied the effects of the neurotoxin nicotine on the adolescent brain in a toxicological study using exposure levels typical of occasional to regular smokers. They found alterations in the levels of DNA in multiple regions of the brain, even at the lowest dose tested. The effects persisted at least 1 month posttreatment, with larger effects in females. The researchers concluded that during adolescence, the exposures elicited lasting cellular and neuritic damage at exposures approximately one-tenth of those in regular smokers. They described the adolescent brain as exquisite sensitivity to nicotine neurotoxicity, with potential lasting neurobehavioral damage.
Sisk and Foster (2004) report on a range of hormonal changes during adolescence and point to the remodeling and activation of neural circuits that occur as a result of hormonal influences. These researchers point to the hormonal-brain interactions as a critical element of development. This is directly relevant to Mel, which causes both hormonal disruption and neurotoxicity. They state:

> These influences of hormones on reproductive behavior depend in part on changes in the adolescent brain that occur independently of gonadal maturation. Reproductive maturity is therefore the product of developmentally timed, brain-driven and recurrent interactions between steroid hormones and the adolescent nervous system.

(Sisk and Foster (2004).

The thyroid hormones are well known to have effects on the timing and levels of a wide range of hormones, including reproductive hormones described by Sisk and Foster. The finely tuned and highly susceptible hormonal balance that adolescents’ physiology is working towards makes them especially susceptible to a hormonally disruptive chemical such as Mel.

Quantitative adjustments that incorporate greater safety factors are required in any assessment of risk that contemplates exposing children. In addition, the lack of adequate information regarding potential neurotoxic effects across the age span, and especially in high cognitive functioning, is a critical information gap can be partially addressed by a substantial additional margin of safety. To provide adequate protection, it is necessary that research be carried out that can provide assurances of safety. At present there is no research of this type available on Mel so it is not possible to determine whether there is any safe level of exposure to Mel with respect to hormonal and neurological development. Greater wisdom would be demonstrated by not allowing the use of chemicals such as Mel in situations where children could plausibly be exposed.

We strongly recommended that potential harm to teen workers be evaluated by a team of objective specialists in adolescent pediatric neurology, neurotoxicity, endocrinology, and related fields. They are needed to evaluate the relevance of the toxic effects of Mel to older children, taking into account the unique susceptibilities of adolescents, their physiology, and likely exposure patterns.

It remains to be determined what the impacts of the neurotoxic and hormonally active chemical Mel is on adolescent hormone levels and neurological development may be. However, it is clear that this is an extremely critical sensitive period of development, and that abnormalities in physiology (e.g., levels of hormones) can cause serious disruption of normal growth and development.
Appendix A. Abstracts of select cited studies.

**The effects of solvent exposure on memory and motor dexterity in working children.**
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OBJECTIVES: Children working in vehicle spray-painting, mechanical, and other trade workshops are at significant risk of exposure to organic solvents and, as a result, may be at significant risk of developing clinical and subclinical signs of neurotoxicity. This study reports on the association between exposure to solvents and neurobehavioral performance on a number of non-computerized tests for working children exposed to solvents in comparison with nonexposed working children and nonexposed children at school.

METHODS: A convenience cross-sectional sample of 300 male children aged 10-17 years was recruited for study. The exposed working group and the two nonexposed groups (working and nonworking school) were matched, as far as possible, on geographic location of residence and age. Neurotoxic effects were assessed through a questionnaire and the child's performance on a selection of neurobehavioral tests.

RESULTS: Exposed working children scored worse on the overall neurotoxicity symptoms score (mean=6.8; standard deviation [SD]=3.6) compared with the nonexposed working children (mean=1.3; SD=2.0) and school children (mean=1.2; SD=1.8). Analysis of the non-computerized neurobehavioral tests demonstrated that exposed working children performed significantly worse than the two nonexposed groups on the motor dexterity and memory tests. Results of the mood test showed that exposed working children were more angry and confused than the nonexposed groups.

CONCLUSION: There is an association between exposure to solvents and lower neurobehavioral performance, with significant neurobehavioral deficits among children exposed to solvents in comparison with working children not exposed to solvents and nonworking school children. Memory and motor dexterity appear to be particularly affected in solvent-exposed working children.

**Nicotine is a neurotoxin in the adolescent brain: critical periods, patterns of exposure, regional selectivity, and dose thresholds for macromolecular alterations.**
Abreu-Villaca Y, Seidler FJ, Tate CA, Slotkin TA. Department of Pharmacology and Cancer Biology, Duke University Medical Center, 27710, Durham, NC, USA.
Brain Res. 2003 Jul 25;979(1-2):114-28

In the fetus, nicotine is a neuroteratogen that elicits cell damage and loss and subsequent abnormalities of synaptic function. We explored whether these effects extend into adolescence, the period when most people begin smoking. Beginning on
postnatal day 30, rats were given a 1 week regimen of nicotine infusions or twice-daily injections, at doses (0.6, 2 and 6 mg/kg/day) set to achieve plasma levels found in occasional to regular smokers. We assessed indices of cell packing density and cell number (DNA concentration and content), cell size (total protein/DNA ratio) and neuritic projections (membrane/total protein) in the midbrain, hippocampus and cerebral cortex, three regions known to be vulnerable to developmental effects of nicotine. With either route of administration, nicotine evoked shortfalls in DNA concentration and content, compensatory elevations of total protein/DNA, and reductions in the membrane/total protein ratio. Nearly all of the effects were apparent even at the lowest dose of nicotine and remained fully evident 1 month posttreatment. Although both males and females showed significant alterations, in general the effects were larger in females. Our results indicate that in adolescence, even a brief period of continuous or intermittent nicotine exposure, elicits lasting alterations in biomarkers associated with cellular and neuritic damage. As the effects are detected at exposures that produce plasma concentrations one-tenth of those in regular smokers, the exquisite sensitivity of the adolescent brain to nicotine neurotoxicity may contribute to lasting neurobehavioral damage even in occasional smokers.

Age-related effects of alcohol on memory and memory-related brain function in adolescents and adults.
White AM, Swartzwelder HS. Duke University Medical Center, Neurobiology Research Labs, Veterans Affairs Medical Center, Durham, North Carolina 27710, USA.
Recent Dev Alcohol. 2005;17:161-76

As detailed in this brief review, there is now clear evidence that adolescence represents a unique stage of brain development. Changes in brain organization and function during adolescence are widespread, and include intense rewiring in the frontal lobes and other neocortical regions, as well as changes in a litany of subcortical structures. Recent research suggests that, because of these changes in brain function, drugs like alcohol affect adolescents and adults differently. The available evidence, much of it from research with animal models, suggests that adolescents might be more sensitive than adults to the memory impairing effects of alcohol, as well as the impact of alcohol on the brain function that underlies memory formation. For instance, when treated with alcohol, adolescent rats perform worse than adults in spatial learning tasks that are known to require the functioning of the hippocampus. Alcohol disrupts hippocampal function, and does so more potently in adolescents than adults. In contrast, adolescents appear to be far less sensitive than adults to both the sedative and motor impairing effects of alcohol. While research on this topic is still in its infancy, the findings clearly suggest that adolescence represents a unique stage of sensitivity to the impact of alcohol on behavior and brain function.
fMRI reveals alteration of spatial working memory networks across adolescence.
Schweinsburg AD, Nagel BJ, Tapert SF. Department of Psychology, University of California, San Diego, La Jolla, California, USA.
J Int Neuropsychol Soc. 2005 Sep;11(5):631-44

Recent studies have described neuromaturation and cognitive development across the lifespan, yet few neuroimaging studies have investigated task-related alterations in brain activity during adolescence. We used functional magnetic resonance imaging (fMRI) to examine brain response to a spatial working memory (SWM) task in 49 typically developing adolescents (25 females and 24 males; ages 12-17). No gender or age differences were found for task performance during SWM. However, age was positively associated with SWM brain response in left prefrontal and bilateral inferior posterior parietal regions. Age was negatively associated with SWM activation in bilateral superior parietal cortex. Gender was significantly associated with SWM response; females demonstrated diminished anterior cingulate activation and males demonstrated greater response in frontopolar cortex than females. Our findings indicate that the frontal and parietal neural networks involved in spatial working memory change over the adolescent age range and are further influenced by gender. These changes may represent evolving mnemonic strategies subserved by ongoing adolescent brain development.

Pubertal neuromaturation, stress sensitivity, and psychopathology.
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Normal adolescent development is often accompanied by transient emotional and behavioral problems. For most individuals with postpubertal-onset adjustment problems, there is a resolution by early adulthood and relative stability through the adult life span. But for a minority, adjustment problems escalate during adolescence and portend the development of serious mental illness in adulthood. In this article, we explore adolescent behavioral changes and neurodevelopmental processes that might contribute to stress sensitivity and vulnerability for the emergence of the mental disorders. Of particular interest is the role that hormonal changes might play in the expression of genetic vulnerabilities for psychopathology. Drawing on recent findings from clinical research and behavioral neuroscience, we describe the ways in which postpubertal hormones might alter brain function and, thereby, behavior. It is concluded that there are both activational and organization effects of hormones on the adolescent brain, and these contribute to developmental discontinuities in behavioral adjustment. Implications for adult psychopathology and preventive intervention are discussed.
The neural basis of puberty and adolescence.
Sisk CL, Foster DL. Neuroscience Program and Department of Psychology, Michigan State University, East Lansing, Michigan 48824, USA. sisk@msu.edu <sisk@msu.edu> Nat Neurosci. 2004 Oct;7(10):1040-7.

The pubertal transition to adulthood involves both gonadal and behavioral maturation. A developmental clock, along with permissive signals that provide information on somatic growth, energy balance and season, time the awakening of gonadotropin releasing hormone (GnRH) neurons at the onset of puberty. High-frequency GnRH release results from disinhibition and activation of GnRH neurons at puberty onset, leading to gametogenesis and an increase in gonadal steroid hormone secretion. Steroid hormones, in turn, both remodel and activate neural circuits during adolescent brain development, leading to the development of sexual salience of sensory stimuli, sexual motivation, and expression of copulatory behaviors in specific social contexts. These influences of hormones on reproductive behavior depend in part on changes in the adolescent brain that occur independently of gonadal maturation. Reproductive maturity is therefore the product of developmentally timed, brain-driven and recurrent interactions between steroid hormones and the adolescent nervous system.