



Families Against Mandatory Minimums

F O U N D A T I O N

March 9, 2001

Mr. Michael Courlander
United States Sentencing Commission
One Columbus Circle, N.E.
Washington, D.C. 20002-8002

Dear Mr. Courlander:

I request that I be added to the list of people presenting testimony to the Commission on March 19, 2001. My statement is attached.

Please feel free to contact me at (202) 822-6700 if you have any questions.

Thank you.

Sincerely,

Mary Price



Families Against Mandatory Minimums

F U N D A T I O N

Statement of Mary Price
General Counsel
Families Against Mandatory Minimums
Submitted March 9, 2001

Families Against Mandatory Minimums (FAMM) works to end mandatory minimum sentencing laws and practices. We do so because discretionless sentencing frequently results in draconian penalties that fit neither the crime nor the offender. Over the years we have worked in Congress and before this Commission to bring you the faces and stories of people subjected to mandatory sentences (due either to statutory minimums or guideline offense levels). We have done so out of our belief that sentencing decisions should be made in light of **all the information available**, including how discretionless sentencing affects offenders whose culpability is not measured by drug quantities. Today we once again express our concern that the Commission consider its decisions in light of **all the information available**, this time about Ecstasy. This body is uniquely suited to fashion appropriate penalties, constrained only by the need to increase the existing penalties as directed by Congress. We are deeply concerned that the current proposal to increase Ecstasy penalties does not credit the many objections from the medical and scientific community that calls into doubt a number of the conclusions on which the Commission appears to be basing its decision.

Background on Proposal

Today, this commission is poised to assign new and substantially higher penalties for trafficking in Ecstasy. The proposed amendment responds to the Congressional directive to increase the base offense level for MDMA, MDA, PMA, and MDEA. It does so by amending the drug equivalency table to "make the penalties for these substances comparable to other drugs of abuse." Proposed Amendment to the Sentencing Guidelines, Proposed Amendment: Ecstasy, at 1. Congress did not direct the Commission to raise the penalty level by a given amount, or equate the drugs with a specific drug currently warranting higher penalties.

The Commission proposed originally to equalize the penalties among these drugs and then equate them with heroin, without any explanation or justification for such a remarkable increase. (For example, as originally proposed, the amended level for MDMA would add **twelve** offense levels for 100 grams of MDMA.) Publishing the proposal a mere two weeks prior to the deadline for comments, this Commission merely noted that "Ecstasy (*i.e.*, MDMA, MDEA, MDA and PMA)¹ is similar in its hallucinogenic effect on the user to mescaline, and also has been described

¹ Troubling is the fact that the Commission, *sua sponte*, has chosen to erase penalty distinctions among these drugs, which are different in significant ways and which are currently

as having an added stimulant component It has also been suggested that the drug is neither physically nor psychologically addictive.” Issue for Comment.

Today, the proposal to increase penalties has been scaled back very modestly to equate 1 gram of MDMA, etc. to 500 grams of marijuana, placing the drugs on the continuum between heroin and cocaine.

In the Issue for Comment, this body listed a variety of other drugs to which Ecstasy might be compared, ranging from cocaine to mescaline. The latter drug equivalency would **actually reduce the penalties**, contrary to Congressional directive, given that at present 1 gram of MDMA is equivalent to 35 grams of marijuana while 1 gram of mescaline equals 10 grams of marijuana. It was probably the latter proposal, as appealing as it might appear in light of the Commission’s conclusion that Ecstasy is similar to mescaline, that is in some sense most troubling, insofar as it reveals what appears to be a rather random approach to setting the penalty levels and drug equivalencies. We simply could not figure out how the Commission arrived at the penalty trigger it established and what about MDMA merited such a severe jump, particularly in light of the fact that the overwhelming majority of comments received on this proposal disputed the severity of the increase in light of the information provided by the commission in the Federal Register notice (*see* United States Sentencing Commission, *Public Comment Emergency Amendments, 2001 Amendment Cycle* (January 2001) (including, among others, fifteen letters from doctors, scientists and professors objecting to the original proposal).

One of the chief policy goals of the Commission is to ensure that drug penalties be commensurate with the dangers associated with particular drugs. U.S.S.C., Special Report to Congress regarding Cocaine and Federal Sentencing Policy (April, 1997). All the public comment we read in reaction to the Commission’s first proposal strongly suggested that the penalties proposed were not commensurate with the dangers. We share the Commission’s concern about achieving just sentencing practices. Fairness can only be achieved by considering all sides in an informed, thoughtful and considered process. Therefore, we asked the Commission, as did the National Association of Criminal Defense Lawyers (NACDL), to defer a decision on Ecstasy. The Commission granted NACDL’s request for a deferment so that it could present expert testimony at this hearing.

We are very pleased that the Commission agreed to the additional time to take further testimony, because we believe the Commission has relied on interpretations of scientific studies of the effects of Ecstasy and conclusions drawn from them that are themselves the subject of

treated distinctly under the guidelines. *See* Federal Public and Community Defenders Public Comment at 2 and n.7 (noting the current levels established based on testimony from the DEA and citing DEA, U.S. Dep’t of Justice, *In the Matter of MDMA Scheduling*, Opinion and Recommended Ruling, Findings of Fact and Conclusions of Law of Administrative Law Judge 56 (Docket No. 84-48) (May 1986), discussing differences in cognitive effect between MDA and MDMA).

vigorous debate. The Commission should hear from those scientists and doctors. The scientific community does not agree about the long term neurotoxic effects of Ecstasy or other dangers attendant on its use. A number of submissions also pointed out that the public health and public safety concerns attendant on ecstasy use are much lower than for heroin and cocaine. That much is apparent from the public comments submitted by psychiatrists, physicians, pharmacologists and others published by the Commission.

Medical and Scientific Disputes

The Commission has identified, besides the congressional directive, a number of concerns that drive the proposed penalty levels. A number of the submissions from medical and scientific experts call these assertions into question. I have extracted some in order to underscore our point that there are well-founded disputes surrounding the assumptions and conclusions on which the Commission appears to be relying. In light of those disputes it seems inappropriate to increase penalty levels to such a high degree.

Below are some of the grounds cited by the Commission for increasing the penalties and extracts (nonexhaustive) from some of the submissions received by the Commission in response.

It has "been represented to the Commission that Ecstasy . . . is similar in its hallucinogenic effect on the user to mescaline, and also has been described as having an added stimulant component that can elevate heart rate, blood pressure, and body temperature." Proposed Amendment at 2.

These conclusions are disputed in the comments submitted by Doug Shytle, Ph.D., of the University of South Florida, Department of Psychiatry and Behavioral Medicine. He advised the Commission by his letter of February 4:

I am not aware of any evidence (other than chemical homology) suggesting that Ecstasy has psychological effects on the user similar to the hallucinogenic effects of mescaline. Over the past fifteen years, it has become a well-established scientific fact that MDMA fits into a completely different therapeutic class . . . without the changes in perception in time and space that accompany most other hallucinogenic drugs. **In fact, a recent scientific study . . . reported that MDMA improved measures of sensory gating in human, an effect essentially the opposite one sees with other classic hallucinogens.** (Emphasis added).

David E. Nichols, Professor of Medicinal Chemistry and Molecular Pharmacology at Purdue University, in his letter of February 5, 2001 to the Commission, cites "extensive literature [that] clearly shows that MDMA is in no way comparable to mescaline" either by virtue of its structure, effect, or ability at high doses to produce psychosis.

The drug has a chemical structure similar to methamphetamine. U.S.S.C.,

MDMA Brief Report (February 2001) (Brief Report) at (unpaginated) 2.

Dr. Shytle, in his letter to the Commission, wrote that while MDMA somewhat resembles methamphetamine in its stimulant qualities, it is unclear what that means in terms of health risks. He also asserts that MDMA does not have the physical or psychological addictive potential of methamphetamine, or for that matter, cocaine or heroin.

Dr. Nichols also advised the Commission that while MDMA does have some stimulant effect, it is "approximately only one-tenth that of methamphetamine."

In 1998 MDMA was mentioned in relationship to emergency room visits 1, 135 times, up from 626 times in 1997. Brief Report at 2, citing the Community Epidemiology Working Group review of Drug Abuse Warning Network (DAWN) emergency room mentions.

This statistic appears to be incomplete or at least, not presented in context. The DAWN data for 1999 reveals that 19 percent of all emergency room visits that mentioned a drug or alcohol related cause listed alcohol; 17 percent mentioned cocaine and a mere 0.03 reported MDMA. Letter from Julie Holland, MD, Attending Psychiatrist, Bellevue Hospital, to Michael Courlander (March 3, 2001). Furthermore, a study was recently conducted by Bellevue medical emergency room physicians of hospital ecstasy cases reported to the New York Poison Control Center. There were 191 cases reported between 1993 and 1999 of which 139 cases or 73 percent were mild with little or no toxicity. Most common were reports of increased heart-rate (22 percent); agitation (19 percent) and nausea (12 percent). Only one ecstasy death was reported and that due to hyperthermia. *Id.*

Among the "physical and emotional hazards" . . . associated with MDMA use:

problems similar to those experienced by amphetamine and cocaine users . . . [and] can include muscle tension, involuntary teeth clenching, nausea, blurred vision, faintness, and chills or sweating;

confusion, depression, sleep problems, anxiety, and paranoia during, and sometimes weeks after, taking the drug.

MDMA Brief Report at 3.

Dr. Holland, Attending Psychiatrist in the emergency department at Bellevue Hospital writes that in her five years there she has routinely treated "every kind of casualty to drug and alcohol abuse imaginable: psychosis, severe depression, violence, suicide attempts, homelessness

and self-neglect. At least three-quarters of the patients I see on any given shift are exacerbating, if not causing, their psychiatric illness by using alcohol and cocaine. Less than one percent of these substance-induced psychiatric disorders are due to MDMA."

[f]atalities associated with MDMA . . . [from] dehydration, hyperthermia, heart or kidney failure.

Brief Report at 3, *citing*, NIDA Notes, *Facts About MDMA (Ecstasy)*, National Institute on Drug Abuse, NIH Publication Number 99-3478 (November 1999).

Dr. Holland points out in her statement to the Commission of March 3, that DAWN data reveals that between 1994 and 1998, 2,601 people died from methamphetamine while only 27 deaths were attributed to MDMA. In 1999, 4,705 people died from heroin poisoning, while 9 people died secondary to MDMA use.

"Also of great concern [are] the long term effects of MDMA on serotonin sites within the brain." Brief report at 3. Distilling the NIDA Notes, the Brief Report reported that brain scan comparisons showed that MDMA users had significantly reduced numbers of serotonin transporters and that loss corresponded to greater drug use. A baboon study demonstrated actual loss of serotonin nerve endings. The researchers who conducted the baboon study compared human and non human users in memory tests finding significant impairments in visual and verbal memory. "Whether loss of these serotonin sites and the corresponding impairment are permanent is unknown at this time. However, one study involving squirrel monkeys indicates that some damage to serotonin sites persists at least seven years after exposure to the drug."

Brief Report at 4, *citing* report published by Hatzidimetriou, G, McCann, U.D., Ricuarte, G.A. in *Journal of Neuroscience* 1999 Jun 15; 19(12): pp. 5096-5107.

The Criminal Division of the Department of Justice also points to concerns about brain damage, asserting without identifying the literature, that

scientific studies have established that MDMA is neurotoxic and destroys serotonin in the brain. It causes the death of brain cells by producing both high body temperature and high blood/brain levels of the drug. The damage this drug can produce is significant and long term.

Letter from Michael Horowitz, Chief of Staff, United States Department of Justice, Criminal Division. (February 9, 2001) at 2.

The neurotoxic effects of MDMA, probably the most frightening potential danger, are also

disputed in the medical community. See James P. O'Callaghan, Ph.D., Head, Molecular Neurotoxicology Laboratory, Centers for Disease Control and Prevention - NIOSH, *Defining Neurotoxicity: Lessons from MDMA and Other Amphetamines* (attached). He concludes that while MDMA targets the serotonin-containing neurons and may deplete serotonin, that is not synonymous with brain damage. "Despite nearly two decades of research on the neurotoxic properties of substituted amphetamines, including MDMA, no definitive data have been obtained to indicate that these compounds are in fact neurotoxic to man." O'Callaghan at 14.

Similarly, Charles S. Grob, M.D., Director of Child and Adolescent Psychiatry at Harbor-UCLA Medical Center disputes the conclusion that MDMA causes permanent brain damage. In his paper, *Deconstructing Ecstasy: the Politics of MDMA Research*, published in *Addiction Research*, 2000, Vol. 8, No. 6, he calls into question the conclusions of such research. Dr. Grob's paper cites flaws in research using monkey models that "neglect interspecies differences in pharmacokinetics and drug metabolism" (at 564) and cites the ongoing "debate over the clinical relevance of the MDMA neurotoxicity data." (At 567). "A further cause for concern has been the lack of reports emerging of the long-term effects of high dose MDMA on non-human primate behavior." Noting the seven-year monkey study that showed altered serotonin sites, he wrote that it was puzzling that no information was made available about the monkey's behavior in that time period in light of the fact that "[t]he field of evolutionary biology is rich with examples of how primate research models have furthered our understanding of the relationship between altered neurotransmitter function and animal behavior." Grob at 567. He also identified other methodological irregularities in studies as well as "discrepancies between how studies were actually conducted and how there were reported in the literature." Grob at 571.

Conclusion

While this is by no means an exhaustive examination, as you can see from this short survey of the materials you have received regarding the proposed amendment, many of the conclusions presented in the Commission's brief report are disputed. FAMM does not recommend that this Commission resolve these very difficult disputes within the scientific community. Rather we ask that you recognize that the medical and scientific community are not of one mind about the dangers attendant on the use of MDMA and many in the community do not believe the drug to be as dangerous as heroin, cocaine, methamphetamine or even mescaline. In light of these deep and fundamental disagreements, we urge that you refrain from increasing penalties to such a drastic extent.

If the Commission is not convinced that penalizing MDMA at or above cocaine overstates the danger, certainly setting such a drastic penalty in light of the dearth of agreement about those dangers should promote a more moderate approach. Disputed studies and unsupported claims weave very brittle reeds on which to base such drastic increases in penalties. FAMM urges you to step back from such sweeping changes in the penalty levels given that some of the most basic assumptions on which the Commission appears to rest its decision are at best disputed, if not unsupported.

Furthermore, in light of the concerns we have expressed about how the Commission arrived at the proposed penalties we make the following recommendations:

1. Permit members of the public to attend what have heretofore been *ex parte* briefings by DEA, NIDA, and the Customs Service. In the alternative, make those briefing materials available to those of us in the public who wish to comment on proposed drug guideline amendments. Casting sunshine on this process can certainly improve it and is likely to result in a more informed public, one that can be more confident of the outcomes. Help us understand how you arrive at decisions. Why does Ecstasy warrant a place in the drug equivalency table at or near heroin and cocaine. What are the criteria you apply assigning penalty levels?

2. Actively encourage and invite experts outside the Justice Department to address the Commission when considering information beyond the expertise of this body. In this case, it appears that the Commission heard from only one side of what is appears to be a vigorous debate in the medical community over the harms posed by Ecstasy. It can only improve decisions to invite other respected voices to address questions, particularly when so much is at stake. For example, NACDL had hoped to secure an invitation from the Commission for Dr. James P. O'Callaghan, but was unable to secure one. Dr. O'Callaghan is the head of the Molecular Neurotoxicology Laboratory at the Centers for Disease Control, National Institute of Occupational Safety and Health. Dr. O'Callaghan is a leading expert on Neurotoxicology and has conducted research and written extensively on the subject of neurotoxicity and MDMA. He has concluded that no definitive data exists so far indicating that MDMA and other substituted amphetamines are neurotoxic (that is, cause brain damage) to humans. He would have addressed his remarks to the issue of serotonin neurotoxicity and brain damage and discussed his conclusions from original research on laboratory animals, that brain damage only follows massive doses of MDMA in laboratory animals and that damage does not implicate the serotonin nervous system. An invitation was necessary because he works for another federal agency. This Commission would have benefitted from his contribution.

3. Revisit drug sentencing policy in light of the concerns raised by this proposed amendment. It would be a good time to reassess criteria for assigning penalty levels and judging relative penalties for different substances.

DEFINING NEUROTOXICITY: LESSONS
FROM MDMA AND OTHER AMPHETAMINES

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“This is your brain (an egg); this is your brain on drugs (egg in frying pan).” This “fried egg/fried brain” analogy has long been used to depict the adverse consequences of drug use. But just what are the neurotoxic effects of drugs used in a recreational or a therapeutic context? Clearly, in the field of MDMA research, the term “neurotoxicity” has been very broadly applied to describe the effects of the drug in both experimental animals and man. Unfortunately, there has been very little effort to define what is meant by “MDMA neurotoxicity” much less to distinguish MDMA’s “neurotoxic” actions from its potential to cause neuropathological effects, i.e. effects associated with degenerative disorders of the nervous system. In short, everybody talks about drug-induced neurotoxicity but little attempt is made to define it in terms meaningful to the human condition. In this chapter I will briefly address specific aspects of the MDMA neurotoxicity issue by looking at definitions of this term, as well as some different types of effects of MDMA in animals (and humans), and I will talk about functional outcomes. I won’t address dosage regimen, *per se*, but I will touch on some cross-species extrapolation issues.

Brain damage vs. neurotoxicity:

So just what is neurotoxicity in the context of the effects of MDMA use? For example, can this drug damage the brain? For that matter, just what is brain damage and can chemicals/drugs damage the brain? These all are relevant issues with respect to

understanding potential risks associated with the use of MDMA or any other agent that affects the nervous system.

When one speaks of brain damage this is usually equated with neuropathology. Thus, traumatic injury or neurological diseases such as Alzheimer's, Parkinson's, Huntington's or multiple sclerosis all have distinct neuropathological underpinnings defined by changes in brain cells viewed under a microscope (Adams and Duchen, 1992; Olanow and Lieberman, 1992). These neuroanatomical abnormalities serve as the structural (brain cell) basis for the functional deficits associated with a given condition. No one will argue that the neuropathological effects underlying the devastating symptoms associated with diseases or trauma of the nervous system do NOT constitute brain damage. Likewise, on the surface, it would seem safe to assume that acute or long-term administration of MDMA would not be linked to underlying neuropathology (brain damage) in the absence of some neurological symptoms. Unfortunately, this assumption would be erroneous on at least two counts. First, owing to the functional reserve of the nervous system, damage or even near complete destruction of a given brain area is not necessarily associated with loss of brain function. For example, in victims of Parkinson's disease, loss of upwards of 70% of the target neurons is required before characteristic symptoms emerge (Jellinger, 1987). A second consideration is the fact that damage to the putative target of MDMA, the serotonin-containing neurons, may not be obvious due to our lack of understanding as to the function of this component of the nervous system. Thus, it is possible that repeated administration of MDMA over long periods of time may result in subtle brain pathology (damage) and such damage eventually may eventually be

manifested by subtle changes in mood , appetite and sexual behavior, to name a few effects associated with the serotonergic nervous system (Meltzer, 1990; Curzon, 1990; Gorzalka et al., 1990).

When one encounters the term neurotoxicity, this usually is in reference to the effects of chemical exposures in the environment (Luthman et al., 1995) or workplace (Costa and Manzo, 1998), or with self-administration of drugs of abuse (Erinoff, 1993). The specter of chemical-induced carcinogenesis and birth defects has long dominated public perception of the hazards of exposure to specific chemicals and drugs (the “lumps and stumps” mentality). There is, however, more than ample evidence in the literature for the propensity of all classes of chemicals to damage the developing (O’Callaghan and Miller, 1989) and adult nervous system (O’Callaghan, 1993; O’Callaghan et al., 1995), as well as to cause cancer and birth defects. Viewed in these terms, neurotoxicity is synonymous with chemical-induced brain damage. This does not discount the fact that chemicals and drugs have actions on the nervous system that change its biochemistry, indeed, by design that is how drugs achieve their therapeutic actions. Yes, unwanted short to long-term changes in brain chemistry can be viewed as “neurotoxic” because these changes may represent undesired effects of the compound (ethanol would certainly fit into this definition) (O’Callaghan, et al., 1995). Viewed in these latter terms, however, neurotoxicity cannot be equated with brain damage in the absence of evidence for neuropathology. This is the crux of the arguments surrounding the effects of MDMA (see below). For the purposes of the arguments put forth here, a chemical will be considered to be neurotoxic if it causes brain damage.

Neurotoxic episodes in man have been well documented following the ingestion of tainted food (e.g. domoic acid)(Perl et al., 1990), the application of tainted acne medication (triethyltin)(Kimbrough, 1976) or the exposure to industrial solvents and metals to name a few (e.g. mercury and carbon disulfide)(Costa and Manzo, 1998). All of these incidents were associated with deaths and were linked to the neuropathological effects of the offending agent. It is not a question as to whether chemicals are neurotoxic but rather which chemicals preferentially attack the nervous system and at what exposure levels. Moreover, owing to the extreme cellular complexity of the nervous system, one cannot predict which brain area or cell type will be vulnerable to a given neurotoxic chemical or whether symptoms of exposure will be overt or hidden (see O'Callaghan, et al., 1995). Nor can one assume that the neurotoxic effects of a drug are just dose-related extensions of its pharmacology. For example, therapeutic dosages of a drug known as MK-801, an anti-seizure medication, antagonize the toxic actions of excessive levels of the neurotransmitter glutamate by blocking its receptors throughout the brain (Monaghan et al., 1989). At high dosages, MK-801 has been shown to destroy neurons in a small area of cerebral cortex, a brain region unrelated to the sites of its therapeutic actions (Fix et al., 1994; 1995). By analogy, even though the psychostimulant actions of MDMA may be mediated through the serotonergic nervous system, there is no reason, a priori, to assume that serotonergic neurons would be affected at doses that might be toxic to other brain systems (or other organs). All of this may seem confusing but the facts of the matter are dictated by our neurobiological make-up which, in turn, predicts the following:

- 1) chemicals/drugs can damage the brain; 2) areas of the brain that mediate the desired

pharmacological effects may not be the areas vulnerable to toxicity and 3) subtle brain damage can occur in experimental animals and in man in the absence of overt symptoms.

How do you detect subtle damage of the brain?

If one accepts the notion that chemicals can damage the brain and that damage constitutes neurotoxicity, then all that is needed to assess neurotoxicity are the appropriate techniques. As with the evaluation of traumatized or diseased brains, neuroanatomical methods have remained the dominant means for detection and characterization of neurotoxicity (see O'Callaghan et al., 1995). Where cells are killed outright by the offending agent, it is possible to visualize the damaged areas with tissue stains that have been in common usage for more than a century. Of course, under these circumstances, the functional deficits associated with the loss of cells already may have provided the clues to point to a neurotoxic exposure. This situation is unlikely to describe the real-world situation. Here, the greatest concern is directed toward detecting and preventing the cumulative damage that occurs following protracted exposures to chemicals or drugs whose damage is not detected using traditional neuroanatomical stains. Examples would be drugs or chemicals that kill only a few cells, where the surviving cells would be in far greater numbers than those that were destroyed (i.e. like looking for the "needle in the haystack"). Perhaps an even more likely situation would be chemical destruction of parts of neurons with sparing of the nerve cell itself. This is the case put forth for MDMA neurotoxicity (see below). Under both of these scenarios, the selective and discrete nature of neurotoxic effects dictates the need for special

techniques/indicators to identify cells damaged (but not necessarily killed) by a given neurotoxic agent (O'Callaghan and Jensen, 1992). This is not an easy task because, as mentioned above, while the targets of neurotoxic insults may be limited to a very small area of the nervous system, any area of the nervous system may be affected. For the small drop of damaged brain to be detected within the sea of unaffected tissue, requires an indicator of neurotoxicity that possess several features, as follows: 1) it must reveal diverse types of injuries to any area of the nervous system, 2) it must be sensitive to low levels of damage, 3) it must be specific to the damage (neurotoxic) condition so that therapeutic effects of drugs are not scored positive. Succinctly stated, the ideal neurotoxicity endpoint would be an indicator of damage at any level anywhere in the nervous system that would not pick up therapeutic actions of drugs (O'Callaghan et al., 1995).

The propensity of the damaged brain to cause enlargement of a specific cell type known as the astrocyte and for damaged neurons to become impregnated with silver (argyrophilia) are two of only a handful of generic indicators of brain damage, regardless of the causative agent (O'Callaghan, 1993; O'Callaghan and Jensen, 1992). Astrocyte enlargement, known as astrogliosis, refers to the reaction of this brain cell type to all types of brain injury (O'Callaghan, 1993). The hallmark of this response is the accumulation of a protein within astrocytes known as glial fibrillary acidic protein (GFAP). Increases in GFAP, therefore, serve as an indicator of astrogliosis and, by extension, of neurotoxicity. Increased GFAP expression can be examined in slides of brain tissue with antibodies that recognize this protein. Alternatively GFAP levels in

samples of brain tissue can be measured by sensitive immunoassays. Elevations in GFAP are already widely accepted as indicators of brain damage associated with neurological diseases such as Alzheimer's and multiple sclerosis. More recently, enhanced expression of GFAP has been validated as an indicator of neurotoxicity by using a wide variety of prototype chemical neurotoxicants (O'Callaghan, 1993; O'Callaghan, et al., 1995). These include agents that damage many regions of the brain and many different cell types within a brain region, as would be expected to occur under "real-world" conditions. Moreover, increases in GFAP reveal subtle damage to neurons, such as loss of nerve endings, under conditions where traditional neuropathological stains fail to reveal the damage. Importantly, GFAP levels do not change with pharmacological agents administered at therapeutic dosages. Thus, GFAP assessments fulfill the desired requirements for an indicator of neurotoxicity.

As with the increases in GFAP associated with chemical-induced neurotoxicity, staining of brain cells with special silver degeneration stains can be used to show regions and cell types damaged by neurotoxic exposures (O'Callaghan and Jensen, 1992). Silver stains are not as extensively validated as GFAP as indicators of neurotoxicity. Where silver stains have been used, however, they show at least equal sensitivity to GFAP, they reveal sites of damage in the absence of overt cytopathology as assessed by traditional neuroanatomical methods and drug effects do not screen positive. When analysis of GFAP is coupled with mapping of argyrophilia using silver stains, there is a remarkable correspondence between the regional and cellular patterns of neurotoxicity revealed by the two techniques. Thus, it is likely that the two approaches to neurotoxicity assessment

represent specific and sensitive methods for the assessment of all types of neurotoxic exposures.

What is serotonin neurotoxicity?

In light of the points made above, it would seem sensible to apply GFAP assays and silver degeneration stains to determine whether MDMA is neurotoxic. This has been done in a number of laboratories and I will elaborate on some of the findings below. First, however, it is useful to review the context within which MDMA is considered to be neurotoxic. In almost all studies using experimental animals and humans, MDMA is described as a serotonin neurotoxin (see McKenna and Peroutka, 1990; Steele et al., 1994; Green et al., 1995). What does this mean? Serotonin neurotoxicity implies that MDMA damages the serotonergic nervous system. Because MDMA was known to release serotonin from the nerve endings of serotonin containing neurons in experimental animals, these serotonergic neurons were viewed as the presumed targets of any neurotoxic effects of the drug. Indeed, subsequent measurements of serotonin levels after administration of high dosages of MDMA to rats showed weeks-long decreases in this neurotransmitter. Further, measurements of the enzyme that catalyzes the synthesis of serotonin (tryptophan hydroxylase) and of the protein that transports the released serotonin back into the nerve endings (serotonin transporter) also showed reductions as a result of high doses of MDMA. Because these three constituents of serotonin nerve endings all were reduced for long periods of time (weeks to even months) as a result of

large doses of MDMA, these changes were viewed as evidence of serotonin neurotoxicity, i.e. MDMA-induced brain damage (see reviews by, McKenna and Peroutka, 1990; Steele et al., 1994; Green et al., 1995; Sprague, et al., 1998). There is little argument that the protracted decreases in the constituents of serotonergic neurons resulting from the acute or chronic administration of MDMA are not drug-like (subjective) actions of the compound that serve as the basis for its self-administration. Moreover, the persistent nature of the decreases in these serotonergic endpoints could be considered manifestations of toxicity, at least at a metabolic level within serotonergic neurons. Over the past decade, however, there has been broad recognition of the malleability of the adult nervous system. This "plasticity" certainly extends to the serotonergic nervous system and to its components affected by MDMA. For example, it is now known that treatment with antidepressants such as paroxetine or fluoxetine can decrease the serotonin transporter (Piñeyro et al., 1994) as can a condition that does not even involve exposure to a drug: a food restriction diet (Huether et al., 1997). Pharmacotherapy with antidepressants such as fluoxetine (Prozac®) or dieting is not conditions one often associates with neurotoxicity. Because MDMA and Prozac share the propensity to decrease the serotonin transporter suggests that MDMA can be viewed as much as an antidepressant agent as a "serotonin neurotoxin." Taken together, these observations indicate that changes (even long-term changes) in markers of serotonergic neurons are likely a reflection of neuronal plasticity, i.e. adaptive changes that occur in response to drug therapy in an otherwise intact neuron. Thus, alterations in parameters associated with the functioning of serotonin neurons can not be taken as evidence of neurotoxicity, in the absence of evidence for serotonin neuron pathology. Not only are such "markers"

of serotonergic neurons not useful as stand-alone measures of neurotoxicity, it also is quite likely that current pharmacotherapies may induce changes in these markers and that such changes would be the expected effects of the long-term therapeutic actions of these drugs.

Application of silver stains and GFAP analysis for the assessment of MDMA-induced neurotoxicity

As noted above, one way to resolve the controversy as to whether MDMA is neurotoxic to serotonin neurons would be to use sensitive and selective indicators of neurotoxicity such as silver stains and GFAP analysis (O'Callaghan and Jensen, 1992). When a dose of MDMA (20 mg/kg) that caused 50% decreases in brain serotonin was administered to the rat, it failed to increase GFAP or result in silver staining at any time point after dosing (O'Callaghan and Miller, 1993). Daily dosages of up to 30 mg/kg for a week also did not increase GFAP (O'Callaghan and Miller, 1993). Only when given at fairly enormous dosages to the rat (4 x 50 mg/kg over 24 hours) was evidence of damage obtained (O'Callaghan and Miller, 1993). Even under these circumstances, however, increases in GFAP and silver staining were observed in the cortex but the damaged areas were not those associated with serotonin neurons (O'Callaghan and Miller, 1993; Jensen et al., 1993). These findings indicated that only massive doses of MDMA can cause damage to the brain of the rat and that the damage that occurs is not related to the serotonin nervous system. The implication of these findings is two-fold: 1) changes in markers of serotonin neurons can occur independent of damage to these neurons and 2) large doses of MDMA are required to damage the nervous system of the rat, approximately 100 times the human dosage taken in a recreational context.

One easy explanation for the failure to see damage to serotonin neurons after MDMA, as assessed by assaying GFAP or using silver stains, was that the techniques were not sensitive enough. To address this issue, the known serotonin neurotoxin, 5,7-dihydroxytryptamine, was administered to the rat at a dosage that produced decreases of serotonin equivalent to those seen with MDMA. This resulted in large increases in GFAP (40-100%) in the areas of the brain where serotonin was decreased and these effects were accompanied by silver staining (O'Callaghan and Miller, 1993). These findings indicate the sensitivity of GFAP and silver staining as indices of chemical-induced damage to serotonin neurons. Thus, hallmarks of brain damage occur after damage to serotonin neurons but are absent following administration of very high dosages of MDMA.

Lessons from other compounds and from man.

Lessons learned using experimental animals don't always apply to man, therefore, the absence of evidence (negative data) cited above is not evidence for absence of neurotoxic effects of MDMA in man. In no small measure this often is why sub-human primates are used in an attempt to model more closely the effects presumed to occur in humans.

Unfortunately, different species of sub-human primates also provide different responses to drugs, including MDMA (compare Ricaurte et al., 1988 with Insel et al., 1989). There are, however, lessons that can be learned from human exposures to other compounds that can be applied to MDMA. These compounds are 1-methyl-4-phenyl-1,2,3,6-

tetrahydropyridine (MPTP), methamphetamine and dexfenfluramine. In the early 1980's a group of individuals self-administered what they assumed was an analogue of meperidine (a synthetic narcotic). The compound administered turned out to be MPTP, an unintended contaminant that had devastating consequences: many of the individuals exposed to MPTP developed symptoms of Parkinson's disease (see review by Sayre, 1989). Subsequent research clearly demonstrated that MPTP damaged dopamine-containing neurons, the same ones affected in Parkinson's disease. The MPTP episode raised the specter that similar damage would occur in another cohort of humans, methamphetamine users, because methamphetamine acts on the same dopamine neurons damaged by MPTP and Parkinson's disease. Given the widespread usage of methamphetamine in the 1960's and 1970's, the potential for this drug to have damaged dopamine neurons should now be manifested with age, as is the case for Parkinson's disease (Langston et al., 1992). Because the prevalence of Parkinson's disease has not increased over the intervening decades suggests that methamphetamine is unlikely to have had a neurotoxic effect on human dopamine neurons. A recent study of humans exposed to methamphetamine (Wilson et al., 1996) bears more directly on this issue and provides data more relevant to human MDMA users. This study involved post-mortem examination of brains from verified methamphetamine users. Marked decreases in markers of dopamine neurons were found in these brains including, dopamine, the enzyme that catalyzes its formation (tyrosine hydroxylase) and the dopamine transporter. If the decreases in these markers were a reflection of damage to dopamine neurons, then this would have been manifested as symptoms of Parkinson's disease prior to death. None of these individuals had such symptoms. Thus, as was the case for markers of

serotonin neurons in rats (and, recently, humans) exposed to MDMA (McCann et al., 1998), the data for dopamine markers in human methamphetamine users was indicative of an adaptive change in response to the drug rather than a neurotoxic action on the neuron. The anorectic agent, dexfenfluramine, is the final example of a human exposure relevant to MDMA. Although this compound recently was taken off the market due to reports of abnormal heart function, it was also the subject of a controversy involving neurotoxicity (e.g. see McCann, et al., 1997). This stems from the fact that in rats, MDMA and dexfenfluramine have nearly identical actions on serotonin neurons (e.g. see Zaczek et al., 1990). As a consequence, dexfenfluramine, like MDMA, became a suspect "serotonin neurotoxin (e.g. see McCann et al., 1997)." Unlike MDMA, dexfenfluramine or its racemate, fenfluramine, have been taken by millions of patients worldwide for 20 years. Extensive post-marketing patient surveillance has yet to reveal any effects of dexfenfluramine that can be linked to adverse effects on the nervous system (e.g. see Guy-Grand et al., 1989). The above data for human exposures to methamphetamine and fenfluramine are consistent with results of research on these agents using experimental animals. They indicate that these drugs have the potential to alter biochemical markers of dopamine and serotonin neurons without causing neurotoxicity. Given the similarities between the effects of these compounds and MDMA, it is likely that we can infer that MDMA shares similar actions in man.

Despite nearly two decades of research on the neurotoxic properties of substituted amphetamines, including MDMA, no definitive data have been obtained to indicate that these compounds are in fact neurotoxic to man. This interpretation of existing data does

not constitute an endorsement of the recreational or therapeutic use of these compounds. Rather, it is a call for continued research on the adaptive responses that these compounds engender in their target neurons. If we are to understand the potential for these drugs to cause neurotoxicity, then we must understand the significance of their long-term effects in relation to their potential to damage the nervous system.

References

- Adams, J.H. and Duchen, L.W.: Greenfield's Neuropathology, 5th Edition, Oxford University Press, Oxford, 1992.
- Costa, L.G. and Manzo, L.: Occupational Neurotoxicology, CRC Press, Boca Raton, 1998
- Curzon, G.: Serotonin and appetite. Ann. NY Acad. Sci. 600: 521-531, 1990
- Erinoff, L.: Assessing neurotoxicity of drugs of abuse. NIDA Res. Monograph 136, NIH publication No. 93-3644, U.S. Government Printing Office, 1993.
- Fix, A.S., Long, G.G., Wozniak, D.F., Olney, J.W.: Pathomorphologic effects of N-methyl-D-aspartate antagonists in the rat posterior cingulate/retrosplenial cerebral cortex: a review. Drug. Dev. Res. 32: 147-152, 1994.
- Fix, A.S., Wrightman, K.A. and O'Callaghan, J.P.: Reactive gliosis induced by MK-801 in the rat posterior cingulate/retrosplenial cortex: GFAP evaluation by sandwich ELISA and immunocytochemistry. Neurotoxicology 16: 229-238, 1995.
- Gorzalka, B.B., Mendelson, S.D., Watson, N.V.: Serotonin receptor subtypes and sexual behavior. Ann. NY Acad. Sci. 600: 435-446, 1990.

Green, A.R., Cross, A.J. and Goodwin, G.M.: Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy").

Psychopharmacology 119: 247-260, 1995

Guy-Grand, B., Apfelbaum, M., Crepaldi, G., Gries, A., Lefebvre, P., and Turner, P.:

International trial of long-term dexfenfluramine in obesity. *Lancet*, Nov. 11: 1142-1145, 1989

Huether, G., Zhou, D., Schmidt, S., Wiltfang, J., Ruther, E: Long-term food restriction down-regulates the density of serotonin transporters in the rat frontal cortex. *Biol. Psychiatry* 41: 1174-1180, 1997).

Psychiatry 41: 1174-1180, 1997).

Insel, T.R.: 3,4-Methylenedioxymethamphetamine ("ecstasy") selectively destroys brain serotonin terminals in Rhesus monkeys. *J. Pharmacol. Exp. Ther.* 249: 713-720, 1989.

Jellinger, K.: The pathology of parkinsonism. In: Marsden, C.D. and Fahn, S. (eds.) *Movement Disorders*, Vol. 2, pp. 124-165, Butterworth Press, London, 1987.

Jensen, K.F., O'Callaghan, J.P., Miller, D.B. and Olin, J.K.: Mapping toxicant-induced nervous system damage with a cupric silver stain: A quantitative analysis of neuronal degeneration induced by 3,4-methylenedioxymethamphetamine (MDMA). In: *Assessing Neurotoxicity of Drugs of Abuse*, NIDA Research Monograph 136, NIH Publication No. 93-3644, ed. By L. Erinoff, pp. 133-154, U.S. Government Printing Office, 1993.

Kimbrough, R.D.: Toxicity and health effects of selected organotin compounds: a review. *Environmental Health Perspectives* 14: 51-65, 1976.

Langston, J.W., Koller, W.C., and Giron, L.T.: Etiology of Parkinson's disease. In: *The*

Scientific Basis for the Treatment of Parkinson's Disease. , The Parthenon Publishing Group, Park Ridge, N.J., pp 33-58, 18992.

Luthman, J., Andersson, H. and Olson, L.: Environmental neurotoxicology: A review on identification and action of neurotoxicants. *Technology: J. of the Franklin Institute* 332A: 151-182, 1995.

McCann, U.D., Seiden, L.S., Rubin, L.J., Ricaurte, G.A.: Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine: a systematic review of the evidence. *JAMA* 278: 666-672, 1997.

McCann, U.D., Szabo, Z., Scheffel, U., Dannals, R.F., and Ricaurte, G.A.: Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings. *Lancet* 352: 1433-1437, 1998.

McKenna, D.J. and Peroutka, S.J.: Neurochemistry and neurotoxicity of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). *J. Neurochem.* 54: 14-22, 1990.

Meltzer, H.Y.: Role of serotonin in depression. *Ann. NY Acad. Sci.* 600: 486-500, 1990.

Monaghan, D.T., Bridges, R.J., Cotman, C.W.: The excitatory amino acid receptors: Their classes, pharmacology, and distinct properties in the function of the central nervous system. *Annual. Rev. Pharmacol. Toxicol.* 29: 365-402, 1989.

O'Callaghan, J.P.: Quantitative features of reactive gliosis following toxicant-induced damage of the CNS. *Ann. NY. Acad. Sci.* 679: 195-210, 1993.

O'Callaghan, J.P. and Miller, D.B.: Assessment of chemically-induced alterations in brain development using assays of neuron- and glia-localized proteins. *Neurotoxicology* 10: 393-406, 1989.

- O'Callaghan, J.P., and Jensen, K.F.: Enhanced expression of glial fibrillary acidic protein and the cupric silver degeneration reaction can be used as sensitive and early indicators of neurotoxicity. *Neurotoxicology* 13: 113-122, 1992.
- O'Callaghan, J.P. and Miller, D.B.: Quantification of reactive gliosis as an approach to neurotoxicity assessment. In *Assessing Neurotoxicity of Drugs of Abuse*. NIDA Research Monograph 136, NIH Publication No. 93-1944, ed. By L. Erinoff, pp. 188-212, U.S. Government Printing Office, Washington, D.C., 1993.
- O'Callaghan, J.P., Jensen, K.F., and Miller, D.B.: Quantitative aspects of drug and toxicant-induced astrogliosis. *Neurochem. Int.* 26: 115-124, 1995.
- Olanow, C.W. and Lieberman, A.N.: *The Scientific Basis for the Treatment of Parkinson's Disease*, The Parthenon Publishing Group, Park Ridge, N.J., 1992.
- Piñeyro, G., Bilier, P., Dennis, T., and de Montigny, C.: Desensitization of the neuronal 5-HT carrier following its long-term blockade. *J. Neurosci.* 14: 3036-3047, 1994.
- Perl, T.M., Bédard, L., Kosatsky, T., Hockin, J.C., Todd, E.C.D. and Remis, R.S.: An outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid, *N. Engl. J. Med.* 322: 1775-1780, 1990.
- Ricaurte, G.A., Forno, L.S., Wilson, M.A., DeLanney, L.E., Irwin, I., Molliver, M.E., and Langston, J.W.: ($\pm$)3,4-Methylenedioxymethamphetamine selectively damages central serotonergic neurons in nonhuman primates. *JAMA* 260: 51-55, 1988.
- Sayre, L.M.: Biochemical mechanism of action of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Toxicol. Lett.* 48: 121-149, 1989.
- Sprague, J.E., Everman, S.L., and Nichols, D.E.: An integrated hypothesis for the

serotonergic axonal loss induced by 3,4-methylenedioxymethamphetamine.

Neurotoxicology 19: 427-442, 1998

Steele, T.D., McCann, U.D., Ricaurte, G.A.: 3,4-Methylenedioxymethamphetamine

(MDMA, "Ecstasy"): pharmacology and toxicology in animals and humans.

Addiction 89: 539-551, 1994.

Wilson, J.M., Kalasinsky, K.S., Levey, A.I., Bergeron, C., Reiber, G., Anthony, R.M.,

Schmunk, G.A., Shannak, K., Haycock, J.W. and Kish, S.J.: Striatal dopamine nerve

terminal markers in human, chronic methamphetamine users. Nature Medicine 2:

699-703, 1996.

Zaczek, R., Battaglia, g., Culp, S., Appel, N.M., Contrera, J.F. and DeSouza, E.B.:

Effects of repeated fenfluramine administration on indexes of monoamine function in

rat brain: Pharmacokinetic, dose response, regional specificity and time course data.

J. Pharmacol. Exp. Ther. 253: 104-112, 1990.