

**WRITTEN STATEMENT: Benzylpiperazine (BZP) Sentencing Guidelines Hearing**

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Mr. Chairman and Members of the Commission, thank you for giving me the opportunity to provide information about the designer drug, benzylpiperazine (BZP). As a Staff Scientist who has worked for more than twenty years at the Intramural Research Program of the National Institute on Drug Abuse, I feel privileged to present evidence-based testimony that may contribute to the important decisions of the Commission. To this end, my colleagues and I have published a number of articles describing the pharmacology of BZP, and related compounds, in peer-reviewed scientific journals.

**Why is BZP abused?**

“Designer drugs” are synthetic compounds that are used as alternatives to illicit drugs. The abuse of designer drugs often increases when illicit drugs are not available. BZP is a designer drug which produces feelings of well-being and increased energy, similar to the effects of amphetamine-related stimulants. BZP exerts its psychoactive effects by elevating concentrations of the chemical messenger (i.e., neurotransmitter) dopamine in brain areas that are associated with pleasure and reward. Repeated administrations of BZP produce repeated increases in dopamine, which can lead to habitual use of the drug, a hallmark feature of addiction.

## **Molecular Mechanism of BZP**

At the molecular level, BZP interacts with transporter proteins on the surface of dopamine nerve cells (i.e., dopamine transporters). Dopamine transporters are channel-like pumps which move dopamine molecules from the outside of nerve cells to the inside. Thus, the normal role of dopamine transporters is to keep dopamine concentrations very low outside of cells. BZP binds to the dopamine transporter and disrupts its function, reversing the normal direction of neurotransmitter flow, thereby dumping large amounts of dopamine out of the cell. This reverse transport process is known as “transporter-mediated release”. Accordingly, BZP is classified as a dopamine releaser, similar to the illicit stimulant methamphetamine. It is noteworthy that BZP also releases the neurotransmitter norepinephrine by interacting with transporter proteins on the surface of norepinephrine nerve cells.

## **Pharmacology of BZP**

The effects of BZP administration in animals and humans are mediated by the release of dopamine in the brain, and the release of norepinephrine in peripheral nerves that project to organs like the heart. Specifically, dopamine release is responsible for behavioral effects of the drug, whereas norepinephrine release is responsible for cardiovascular effects. In laboratory rats, the administration of BZP elicits forward locomotion and repetitive movements (i.e., stereotypy) which mimic the effects of methamphetamine. BZP is about ten-fold less potent than

methamphetamine as a locomotor stimulant. Repeated administrations of BZP cause locomotor sensitization, or reverse tolerance, which is the propensity for the same dose of drug to produce greater effects after repeated dosing. The occurrence of BZP sensitization in rats suggests that some effects of the drug might intensify with repeated dosing in people. Patients admitted to the emergency room after high-dose exposure to BZP may exhibit psychotic symptoms including agitation, paranoia and hallucinations. Laboratory rats can be trained to readily self-inject intravenous BZP. Since most of the drugs that are self-injected by rats are abused by humans, it is likely that BZP has a high potential for abuse. BZP causes marked cardiovascular changes in animals and humans, including increased heart rate, irregular heart rhythms, and high blood pressure. After large doses of the drug, elevated body temperature and multi-organ failure can be life-threatening.

### **BZP and Drug-Drug Interactions**

BZP is often used in combination with other illicit drugs, legal designer drugs, and alcohol. In particular, BZP is taken along with drugs that stimulate the serotonin neurotransmitter system, such as 3-trifluoromethylphenylpiperazine (TFMPP). TFMPP stimulates serotonin receptors and acts as a serotonin releaser. The combination of BZP plus TFMPP has psychoactive effects in humans that are comparable to those produced by the illicit drug 3,4-methylenedioxymethamphetamine (MDMA) or Ecstasy. In fact, prior to the DEA scheduling of BZP, the combination of BZP plus TFMPP was sold as “Legal Ecstasy” in retail shops and on Internet websites. Importantly, BZP inhibits the actions of catalytic proteins (i.e., enzymes) in

the liver which help to detoxify and dispose of other drugs. Because of this inhibitory effect, BZP can impair the metabolism of co-administered illicit drugs or prescribed medications, leading to dangerous drug-drug toxicity. Substantial evidence from animals and humans indicates that drug-drug interactions involving BZP contribute to serious adverse effects, including the occurrence of seizures.

## **Summary**

In summary, BZP is a designer drug with significant risk for producing harmful effects, especially when taken repeatedly, at high doses, or in combination with other drugs. The effects of BZP are very similar to those produced by methamphetamine, though BZP is less potent. Because BZP increases dopamine concentrations in brain areas that are associated with pleasure and reward, the drug has potential for abuse. Cardiovascular stimulation produced by BZP can be dangerous. The ability of BZP to inhibit certain liver enzymes may increase the propensity for drug-drug interactions between BZP and co-administered illicit drugs or prescribed medications, leading to toxicity. Finally, I wish to reiterate my sincere thanks to the Commission for allowing me to provide this testimony.