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## Critical Review Report:

### Metonitazene

(N,N-diethyl-2-[(4-methoxyphenyl)methyl]-5-nitro-1H-benzimidazole-1-ethanamine)

Expert Committee on Drug Dependence

Forty-fourth Meeting

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## Executive Summary

Metonitazene was first synthesized in the late 1950s by a Swiss chemical company in an effort to develop novel opioid alternatives to morphine. Though found to have potent analgesic effects, the clinical development of benzimidazole-opioids was abandoned due to the increased risks of adverse events. Currently, there are no drugs of this class approved for medicinal use.

In vitro studies of metonitazene's activity at the mu-opioid receptor have found it to be between 113-121% that of fentanyl, and 184-340% that of hydromorphone. Not surprisingly, metonitazene produces robust typical mu-opioid receptor agonist pharmacodynamic effects.

The analgesic effects of metonitazene have been studied in preclinical models, indicating a potency of between 30-200 times that of morphine (depending on the administration route and animal model). Metonitazene's respiratory depressant effects have been estimated at 50 times greater than morphine. One clinical investigation of metonitazene from the 1960s was found. This study reported robust analgesics effects but depressed respiration with cyanosis was observed in one-fifth of the patients. Clinical and preclinical data suggest that these pharmacodynamic effects of metonitazene can be reversed by an opioid antagonist.

No studies characterize the abuse potential of metonitazene. Given its chemical properties, metonitazene could lend itself to recreational use through intranasal, smoking, and intravenous means.

Starting in 2019, metonitazene was detected in forensic sampling in Canada, the U.S., and Germany. Findings from post-mortem case reports suggest metonitazene is an adulterant to the heroin supply.

Metonitazene is currently not under national or international controls, though in the U.S. it may fall under tight restrictions due to its structural similarity to other scheduled drugs. Internet retailers openly advertise metonitazene's sale and international availability. Metonitazene can be legitimately purchased from pharmaceutical retailers for research, not for human or veterinary use.

## 1. Substance identification

**A. *International Nonproprietary Name (INN)***

No information could be identified.

**B. *Chemical Abstract Service (CAS) Registry Number***

14680-51-4 free base  
3983-24-2 hydrochloride salt

**C. *Other Chemical Names***

Benzimidazole  
1-[2-(diethylamino)ethyl]-2-(p-methoxybenzyl)-5-nitro- (6CI, 7CI, 8CI)  
N,N-Diethyl-2-[(4-methoxyphenyl)methyl]-5-nitro-1H-benzimidazole-1-ethanamine  
(ACI)

**D. *Trade Names***

Metonitazene is also known as “NIH 7606.”

**E. *Street Names***

Not available

**F. *Physical Appearance***

Metonitazene, has been described as a white or off-white/beige powder, sometimes referred to as crystalline in consistency (Cayman Chemicals, 2020; Krotulski et al., 2021; PubChem, 2020). The free base and the hydrochloride salt appear as a white or colored powder. The citrate salt is described as a crystalline solid (Cayman, 2021a).

Images on the Reddit, on an online discussion forum (Reddit, 2020A) and on a website offering metonitazene for sale (Global B2B Marketplace, 2021) depict metonitazene as white, off-white, or beige powder.

**G. *WHO Review History***

Metonitazene has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO’s attention that this substance is manufactured clandestinely, poses a risk to public health and is of no recognized therapeutic use.

## 2. Chemistry

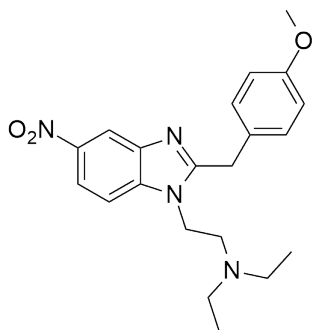
### A. *Chemical Name*

**IUPAC Name:** N,N-diethyl-2-{2-[(4-methoxyphenyl)methyl]-5-nitro-1H-benzimidazol-1-yl}ethan-1-amine

**CA Index Name:** 1H-Benzimidazole-1-ethanamine, N,N-diethyl-2-[(4-methoxyphenyl)methyl]-5-nitro-

### B. *Chemical Structure*

Free base:



**Molecular Formula:** C<sub>21</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub>

**Molecular Weight:** 382.46 g/mol

### C. *Stereoisomers*

There are no stereoisomers described for metonitazene.

### D. *Methods and Ease of Illicit Manufacturing*

Metonitazene is a 5-nitro-2-benzylbenzimidazole belonging to the series of 2-benzylbenzimidazole compounds developed in the late-1950s as opioid analgesics (Ujváry et al., 2021).

Etonitazene, isonitazene, protonitazene and butonitazene are homologues of metonitazene. The substitution at C-4 position of the benzyl moiety with methoxy, ethoxy, isopropoxy and n-propoxy group differentiate metonitazene, etonitazene, protonitazene and butonitazene, respectively. 2-Benzylbenzimidazole compounds can be synthesized via several pathways described in the literature (Hunger et al., 1957, Hunger et al., 1960b, Hunger et al., 1960a, Hoffmann, 1959, K. Hoffmann, 1960, Kim et al., 2011, Renton et al., 2012, Thomas et al., 1997, Bucha et al., 2018, Vandeputte et al., 2021). Although the reagents are readily available on the market and cheap, all syntheses require specialized personnel and need to be carried out in a well-equipped synthetic chemistry laboratory.

There is no information on the actual method and scale of manufacture of 2-benzylbenzimidazoles that have recently been detected although several methods are simple and cost-efficient, not requiring regulated precursors (Ujváry et al., 2021).

### ***E. Chemical Properties***

#### Melting point

The melting point of metonitazene is 76–78 °C as free base and 197–198 °C as hydrochloride salt (Ujváry et al., 2021, Hunger et al., 1960a).

#### Boiling point

No information could be identified.

#### Solubility

Metonitazene is lipophilic, as are its homologues etonitazene and isonitazene. The calculated octanol/water distribution coefficient for metonitazene is  $\log P=3.734\pm 0.936$  at 25 °C (Cayman, 2021b).

Metonitazene free base has a solubility in dimethylformamide (DMF) of 25 mg/mL and of 20 mg/mL in dimethyl sulfoxide (DMSO). In a mixture of DMF and phosphate-buffered saline (PBS) DMF:PBS (pH 7.2) (1:1), the free base is soluble at 0.5 mg/mL and at 10 mg/mL in ethanol (Cayman, 2021b).

Metonitazene citrate is soluble in DMF and DMSO at 10 mg/mL and at 1 mg/mL in PBS (pH 7.2) (Cayman, 2021a).

### ***F. Identification and Analysis***

Synthetic metonitazene was characterized via nuclear magnetic resonance spectroscopy (1H-NMR), high-performance liquid chromatography coupled to diode-array detection (HPLC-DAD), gas chromatography mass spectrometry (GC-MS), and liquid chromatography coupled to time-of-flight MS (LC-QTOF-MS) (Ujváry et al., 2021). Metonitazene free base, citrate salt and metonitazene-*d*<sub>3</sub> citrate are available as reference material from commercial suppliers to assist with the implementation of routine methods of analysis associated with forensic and clinical investigations (Cayman, 2021a).

Analytical methodologies for the identification and quantification of metonitazene in seized and biological sample matrices have recently published and include various chromatographic, spectroscopic and mass spectrometric methods (Vandeputte et al., 2021). Analyses for identification of metonitazene in powders were conducted employing gas chromatography-mass spectrometry (GC-MS), infrared spectroscopy (IR), LC-MS, ion chromatography (IC), NMR (Košmrlj, 2020). Analysis for identification and quantification of metonitazene was also conducted in forensic postmortem cases with an average concentration in blood at  $6.3\pm 7.5$  ng/mL (median: 3.8 ng/mL, range: 0.5-33 ng/mL, n=18) and in urine at  $15\pm 13$  ng/mL (median: 11 ng/mL, range: 0.6-46 ng/mL, n=14) by means of LC-QTOF-MS for qualitative analysis and by LC coupled to triple-quadrupole mass spectrometry (LC-QqQ-MS) for quantitative purpose (Krotulski et al., 2021).

### 3. Ease of Convertibility Into Controlled Substances

It is not known from the literature if metonitazene can be converted into a controlled substance.

### 4. General Pharmacology

#### A. *Routes of administration and dosage*

In the limited clinical studies available, metonitazene has been administered subcutaneously, and intramuscularly to assess its analgesic effects (Ujváry et al., 2021.) Anecdotal reports for discussion forums suggest that the powder can be directly insufflated (though reported to cause significant nasal irritation and burning), or used intranasally (IN) by being dissolved in solution (Reddit, 2015; 2019; 2021A). For IN administration, users recommended between 10-40 mg per occasion. People who use metonitazene also expressed interest in vaping metonitazene solutions (Bluelight.org, 2020; Reddit, 2021A).

Similarly, reports of intravenous (IV) use by dissolving the powder in water or saline solution were also found (Reddit, 2021B). For IV administration users recommend 5-10 mg as “smaller” doses and 75-100mg for experienced opioid users or opioid-dependent individuals. Because of its acidity, users often recommend mixing metonitazene with sodium bicarbonate for IV use (Reddit, 2021B). People who use metonitazene also report or recommend smoking metonitazene using a glass pipe or foil at a recommended dose of 30 mg for an experienced opioid users or someone who is opioid-dependent (Reddit, 2021A).

#### B. *Pharmacokinetics*

Few published reports were found that describe the pharmacokinetics, including metabolite identification, of metonitazene. A recent narrative review failed to find published data on the pharmacokinetics of metonitazene (Ujváry et al., 2021). Krotulski and colleagues (2021) performed metonitazene metabolite discovery using liquid chromatography quadrupole time-of-flight mass spectrometry within 20 forensic postmortem samples. Quantitative confirmation was performed by liquid chromatography tandem quadrupole mass spectrometry. Figure 1 shows their proposed metabolic pathway for metonitazene. Metonitazene is thought to undergo N-dealkylation and O-dealkylation. N-desethyl metonitazene (M.1, C<sub>19</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>) was produced via N-deethylation and was found to be a prominent metabolite in the urine and vitreous samples tested. M.1 is further metabolized thru subsequent N-deethylation to form N,N-didesethyl metonitazene (M.2, C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>). 4'-Hydroxy nitazene (M.3, C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>) is then produced by O-demethylation. 5-Amino metonitazene (M.4, C<sub>21</sub>H<sub>28</sub>N<sub>4</sub>O) is produced via reduction of the nitro moiety (Krotulski et al., 2021).

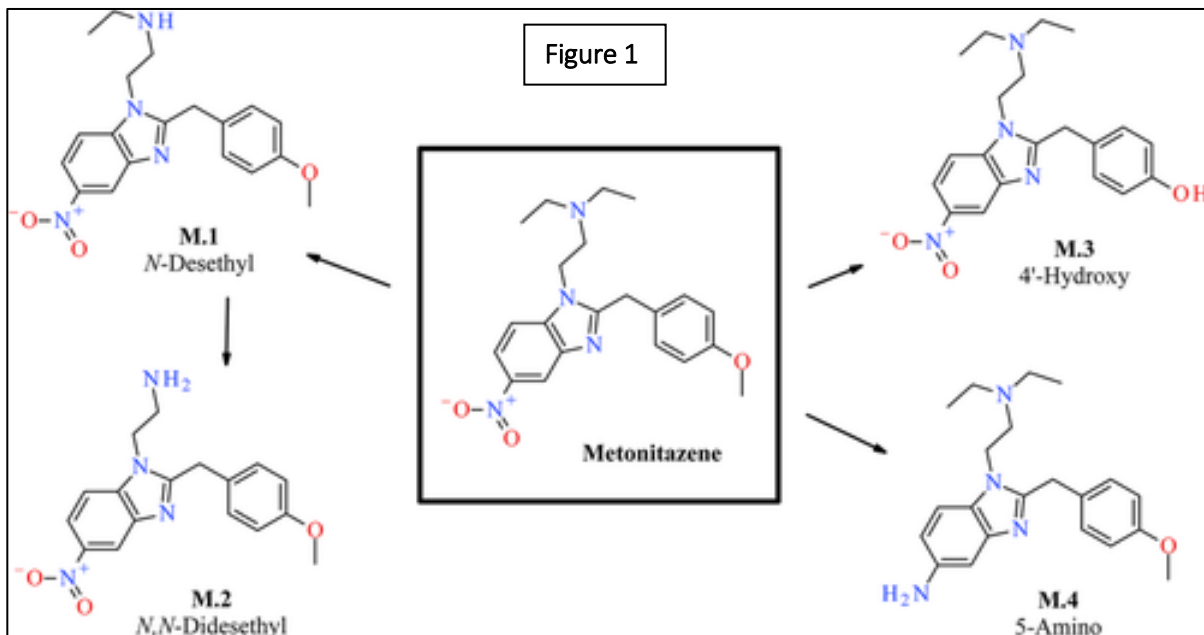


Figure 1: Reproduced with permission from publisher

### C. Pharmacodynamics

As an opioid, pharmacodynamic investigations of metonitazene have focused primarily on affinity for the mu-opioid receptor (MOR) and subsequent characterization of: analgesia/antinociception, abuse potential, and respiratory depression. Ujváry et al., 2021 provide a review the pharmacodynamics of metonitazene and other benzimidazoles. The relevant individual studies described in the review are presented and cited in the current review. The in-vivo pharmacodynamic properties, discussed below, indicate pharmacokinetics required for brain-barrier penetration (i.e., lipophilicity) and abuse potential (i.e., rapid onset of effects).

Opioid Receptor Activity: Vandeputte and colleagues (2021) characterized the mu-opioid receptor activation profiles for five benzimidazole opioids using in-vitro recruitment assays (MOR- $\beta$ arr2 and MOR-mini- Gi. In Figure 2 the mean receptor activation ( $\pm$  standard error) is shown normalized to the maximum response of hydromorphone (a potent opioid analgesic with robust abuse potential (Babalonis et al., 2021).

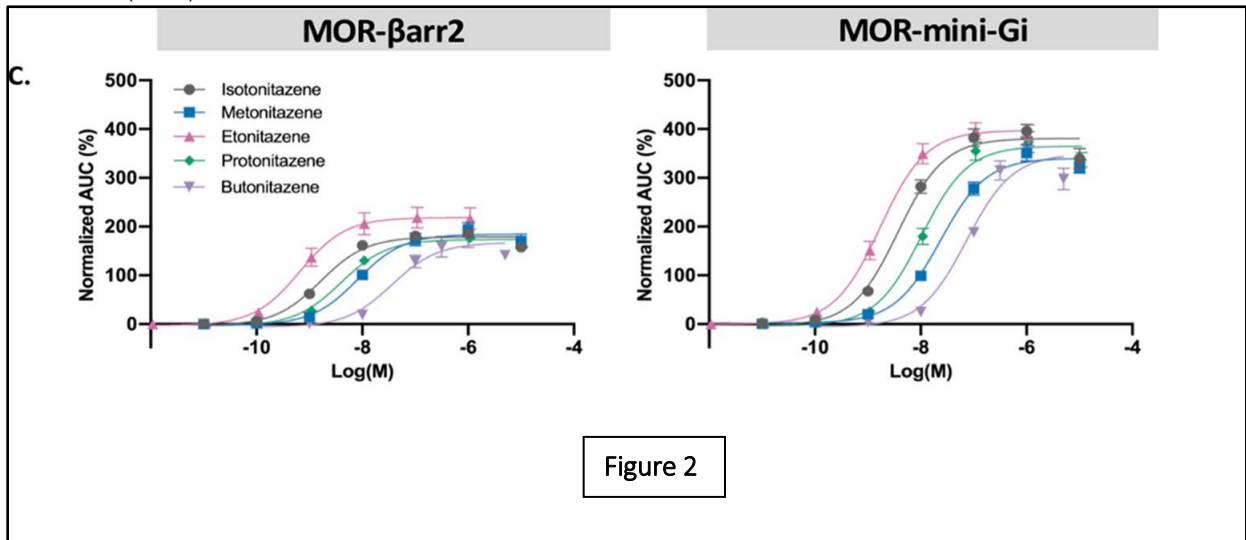


Figure 2

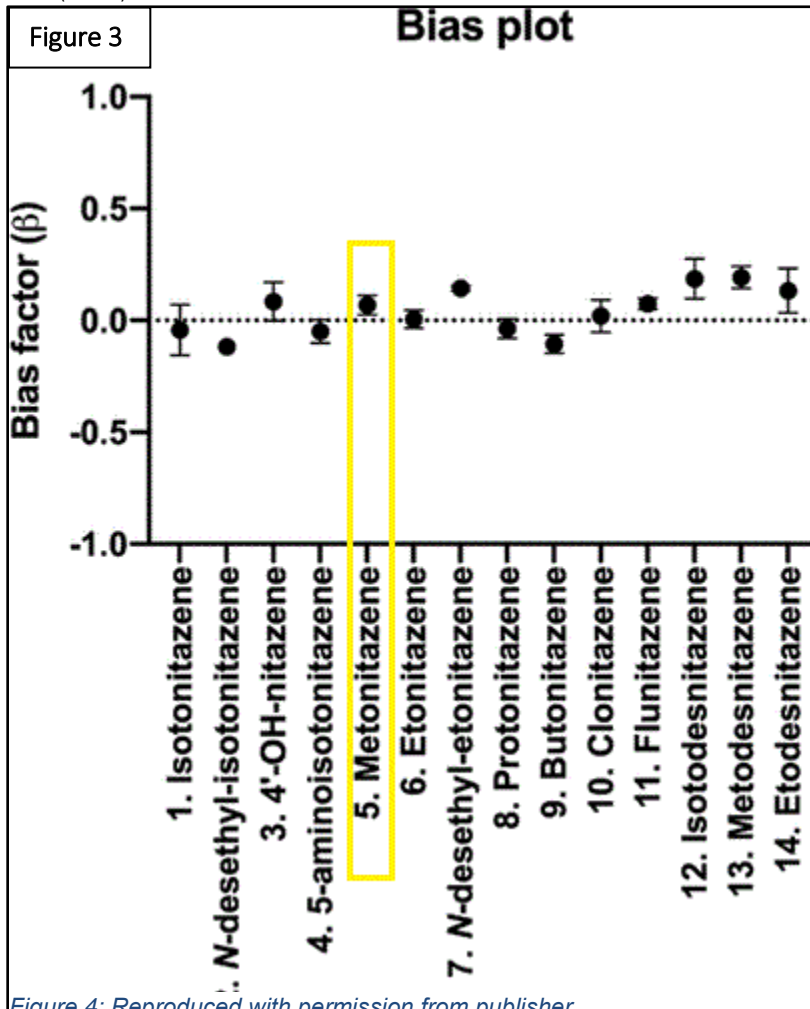
Figure 2: Reproduced with permission from publisher

Shown in Table 1, the investigators calculated the potency (EC<sub>50</sub>) and efficacy (E<sub>max</sub>), of metonitazene, relative to Fentanyl and Hydromorphone (HM). In both assays of  $\mu$ -opioid receptor activation, metonitazene was highly active, with potency and efficacy slightly greater than fentanyl (113-121%) and significantly greater than hydromorphone (184-340%).

Table 1: Relative Potency of Metonitazene to Fentanyl and Hydromorphone (Vandeputte et al., 2021)						
	MOR- $\beta$ arr2			MOR-mini-Gi		
	EC <sub>50</sub>	% Fentanyl E <sub>max</sub>	% HM E <sub>max</sub>	EC <sub>50</sub>	% Fentanyl E <sub>max</sub>	% HM E <sub>max</sub>
<b>Metonitazene</b>	8.14 nM (5.12–12.8)	113 (106–121)	184 (172–197)	23.5 nM (17.7–31.4)	121 (115–126)	340 (326–355)
(95% confidence intervals)						

Figure 3: Reproduced with permission from publisher

The authors (Vandeputte et al., 2021) also found no evidence of significantly biased agonism (i.e., a preference toward  $\beta$ arr2 or mini-Gi recruitment) in metonitazene’s effects at the mu-opioid receptor, as compared to hydromorphone (Figure 3).



Early ex-vivo experiments also compared the activity of metonitazene to the typical opioid, morphine (Gyang et al 1964, Hughes et al., 1975). Metonitazene dose-dependently inhibited the provoked contractions in isolated guinea pig ileum and mouse vas deferens. Metonitazene's potency in preparations of the guinea pig ileum were 50 times greater than morphine, and the effect in mouse vas deferens 100 times greater than morphine. These effects were reversed by nalorphine, a mu-opioid receptor antagonist, kappa-opioid receptor partial agonist (Gharagozlou et al., 2006). There is a lack of data on metonitazene's actions upon the other opioid receptor subtypes (i.e., kappa and delta).

**Analgesia/Antinociception:** In mice, metonitazene's antinociceptive relative potency is estimated at 100 times that of 5 mg/kg morphine (subcutaneous) (Hunger et al., 1957; 1960). Across the preclinical literature that was found (mouse, rat, rabbit), metonitazene's potency was been estimated at 30-100 times (subcutaneous), 15 times (oral), and 200 times (intravenous) that of morphine (Ujváry et al., 2020). In humans, metonitazene hydrochloride was studied in a clinical trial among 363 patients with post-operative or injury-related pain (Bromig, 1958). A translation of the original publication could not be found; however, the results of this study were described by Ujváry and colleagues (2021) in their review. Metonitazene at 1 mg doses (subcutaneous or intramuscular) and produced analgesia, accompanied by sedation, drowsiness, vertigo, confusion, nausea, and vomiting. Depressed respiration with cyanosis was observed in one-fifth of the patients. In one such case, the resulting respiratory depressant effects were so severe it necessitated emergency intervention with nalorphine. The patient recovered, though their pain returned. Based on this investigation it was concluded that metonitazene had 10 times the analgesic potency of morphine but, due to the high risk of adverse effects, further clinical exploration was not pursued.

## 5. Toxicology

Metonitazene is a potent respiratory depressant in rabbits (Gross and Turrian 1957). A 10 µg/kg IV dose resulted in a 50% decrease in respiration frequency; equivalent to that caused by a 0.5 mg/kg dose of morphine. In mice, metonitazene's acute intravenous toxicity (LD50) has been estimated at 50 mg/kg and 100mg/kg orally (Hunger et al., 1957; 1960).

In both preclinical (Gyang et al 1964, Hughes et al., 1975) and human studies (Bromig, 1958) the effects of metonitazene could be antagonized by administration of nalorphine. This implies that the commonly available emergency intervention for opioid overdose, naloxone, should be effective as a reversal agent in cases of over-intoxication events where metonitazene is a contributing drug. It has yet to be investigated if metonitazene produces skeletal muscle rigidity of the chest wall, "wooden chest syndrome," which is a distinguishing characteristic of fentanyl over-intoxication, attributed to its increase of noradrenergic outflow (Burns et al., 2016; Torralva and Janowsky, 2019). However, wooden chest syndrome has been observed in preclinical studies of the structurally related etonitazene (Barnett et al., 1975). Thus, naloxone may only be able to antagonize metonitazene's adverse effects attributable to its actions at opioid receptors.

## 6. Adverse Reactions in Humans

In the U.S, metonitazene was first identified in eight blood specimens associated with postmortem death investigations (Krotulski et al., 2020). Metonitazene was confirmed in 20 forensic post-mortem cases in the U.S. Krotulski and colleagues (2021) detailed these cases, a summary extracted from their report is presented in Table 2. In summary, metonitazene co-occurred most often with fentanyl (55% of cases). In 30% of cases, metonitazene was the sole opioid identified, and within 15% of these cases, it was identified as the cause of death. Most decedents had a history of opioid use disorder and were using/seeking heroin or fentanyl at the time of death. The drug product was most often described as white, off-white, or beige. From witness descriptions, these overdose events presented as typically opioid over-intoxication events, with few uncharacteristic symptoms.

**Table 2: Case history and toxicology results for postmortem cases involving metonitazene. (Krotulski et al., 2021)**

Case	Case synopsis	Date Collected	U.S. State	Metonitazene (ng/ml)	4'-Hydroxy nitazene (ng/ml)	Additional toxicology findings (ng/ml, unless otherwise noted)
1	42 y/o male was found dead in bed with purge fluid coming from nose and mouth. A glass container with beige powder was found.	1/6/2021	OH	Femoral blood: 33 Serum: 18 Urine: 8.4	Femoral blood: negative Serum: positive Urine: 9.8	Butonitazene (femoral blood: 3.2, serum: 2.4, urine 10), <i>N</i> -ethyl pentedrone
2	26 y/o male with a history of heroin use was found unresponsive in a bathroom at his residence. He was found with "bloody purge" coming from his nose.	2/2/2021	IL	IVC blood: 1.6 Urine: positive	IVC blood: Negative Urine: Positive	Fentanyl (12), norfentanyl (0.66), <i>para</i> -fluorofentanyl, 4-ANPP, 6-monoacetylmorphine (2.7), morphine (43), delta-9 carboxy THC (20), diphenhydramine (460), caffeine, quinine, ethanol (16 mg/dl)
3	52 y/o male with a history of drug and alcohol use collapsed at his residence; his roommate was on scene and noted that the decedent was struggling to breathe and become unresponsive. His roommate attempted chest compressions and called emergency medical services (EMS). Upon EMS arrival, the decedent was found to be in asystole. The mouth and nares had vomitus present.	2/3/2021	TN	Femoral blood: 3.1	Femoral blood: negative	Caffeine, ethanol (199 mg/dl)

4	63 y/o male with a history of heroin use was found unresponsive in his locked residence. He was found deceased in his bed with an empty plastic baggie next to him.	2/3/2021	IL	IVC blood: positive (<0.5)  Urine: 0.58  Vitreous: positive (est. 1.1)	IVC blood: negative  Urine: positive  Vitreous: positive	Flunitazene (Positive), 8-aminoclonazepam, 4-ANPP, fentanyl (7.5), norfentanyl (0.85), naloxone, gabapentin (6.8 mcg/ml), caffeine, diphenhydramine (220), quinine
5	34 y/o male with a history of alcoholism, anxiety, and drug use was found by his roommate in his bed deceased. One bottle of clonazepam was located on the nightstand. The roommate had spoken with the decedent the previous day, and the decedent was complaining of stomach pain and vomiting.	2/2/2021	TN	Femoral blood: 0.52	Femoral blood: negative	Methamphetamine (1400), amphetamine (96), alprazolam (5.0), 7-amino clonazepam (11), diphenhydramine (53), citalopram/escitalopram (420), ethanol (15mg/dl)
6	42 y/o homeless male was found unresponsive at a friend's residence. The decedent was found kneeling in a slumped forward position with blood coming from his nose and mouth. A syringe and nylon wrap were in the decedent's hands. A white/yellow powder was recovered from the scene.	2/4/2021	TN	Femoral blood: 8.9  Urine: 14  Vitreous: Positive	Femoral blood: negative  Urine: 8.0  Vitreous: negative	Fentanyl (17), norfentanyl (3.8), 4-ANPP, caffeine, quinine

7	<p>40 y/o male with a history of drug use, HIV/AIDS, and Hepatitis C was found unresponsive at his residence by maintenance staff. The decedent was found in a frog-like position, with a loaded syringe in the upper left thigh. A baggie with pieces of cotton and a metal cap were also found in the bathroom. The nares were congested with pink-tinged fluid.</p>	2/5/2021	TN	<p>Femoral blood: 2.3          Urine: 4.6          Vitreous: positive</p>	<p>Femoral blood: Positive          Urine: 1.2          Vitreous: negative</p>	<p>Fentanyl (5.8), norfentanyl (1.2), acetylfentanyl (0.49), 4-ANPP, methamphetamine (29), caffeine, cotinine, venlafaxine (1300), O-desmethylenlafaxine (390), quinine</p>
8	<p>44 y/o male was found unresponsive at his parent's residence. When the decedent had arrived at the residence earlier in the day, he informed his stepfather that he had used heroin and went outside to sit in a chair. A few minutes later, the stepfather checked on the decedent and he was snoring. Approximately an hour later, the decedent was discovered unresponsive and slumped over in the chair. EMS was called but resuscitative measures were unsuccessful.</p>	2/8/2021	TN	<p>Femoral blood: 1.5          Urine: 4.7          Vitreous: positive</p>	<p>Femoral blood: negative          Urine: 2.7          Vitreous: negative</p>	<p>Fentanyl (16), norfentanyl (1.2), 4-ANPP, methamphetamine (18), amphetamine (6.6), caffeine, cotinine, xylazine, quinine, ethanol (85 mg/dl)</p>

9	59 y/o male with a history of hypertension, atrial fibrillation, status post unknown cardiac procedure, prior stroke, smoking, and drug use (cocaine and oxycodone). He had been complaining of vomiting. He was found dead supine in bed 2 days later with evidence of vomiting at the scene. There was no drug paraphernalia found on the scene.	2/6/2021	FL	Peripheral blood: 2.4  Urine: 46  Vitreous: pos. (est. 1.8)	Peripheral blood: 1.4  Urine: 5.3  Vitreous: negative	Fentanyl (33), norfentanyl (10), 4-ANPP, morphine (41), caffeine, cotinine, gabapentin (31 mcg/ml), fluoxetine (85), norfluoxetine (46), quinine
10	19 y/o male was found unresponsive at friend's residence, with snoring respirations and froth in mouth. Multiple unidentified powders, capsules, and pills were recovered from the scene. Decedent had a history of mescaline, LSD, and molly use. DMT was discovered on the scene.	1/16/2021	WI	Femoral blood (P): 8.7  Femoral blood (P): 7.6	Femoral blood: positive  Femoral blood: positive	N-Ethyl deschloroketamine, etizolam (6.3), alpha-hydroxyetizolam (2.3), tramadol (1100), O-desmethyltramadol (270), 11-hydroxy delta-9 THC (32), delta-9 carboxy THC (200), delta-9 THC (48), caffeine, naloxone

11	43 y/o male with a history of Hepatitis C, heroin use, and past overdose was found unresponsive in the bathroom of his residence by his father. The decedent had recently completed a 3-month rehabilitation program a week prior to death. A syringe, orange cap, clear plastic baggie with a white-colored powder, and a belt were found in close proximity to the body.	11/28/2020	TN	Femoral blood: 6.9  Urine: 35  Vitreous: pos. (est. 1.4)	Femoral blood: positive  Urine: 3.5  Vitreous: positive	Caffeine, cotinine
12	58 y/o male with a history of "heroin" use found deceased in his residence, in a hunched-over position on the floor. A white powdery substance and two cut straws with residue were located near the decedent. Yellow/brown/bloody purge was emanating from the nose.	2/2/2021	IL	Peripheral blood: positive  Urine: 16	Peripheral blood: negative  Urine: 18	Flunitazene (peripheral blood: 0.58, urine: 9.1), 8-aminoclonazepam, flualprazolam, fentanyl (13), norfentanyl (1.5), 4-ANPP, caffeine, diphenhydramine (300), quinine

13	47 y/o male with a history of chronic pain, Hepatitis C, and drug/alcohol use was found unresponsive in the bathroom of his residence by his girlfriend. The girlfriend called EMS and administered two doses of naloxone. Upon EMS arrival, the decedent was discovered in asystole. A small amount of vomit was noted on the floor.	2/20/2021	TN	Femoral blood: 4.0  Vitreous: pos. (est. 0.76)	Femoral blood: negative  Vitreous: positive	Fentanyl (41), norfentanyl (2.4), acetylfentanyl (25), 4-ANPP, caffeine, naloxone, diphenhydramine (72), quinine, ethanol (21 mg/dl)
14	27 y/o male was found deceased in his apartment. The decedent had a previous history of heroin use but was reportedly abstinent for many years. No known significant medical history or trauma at autopsy.	2/8/2021	SC	Femoral blood: 3.5  Urine: 19  Vitreous: pos. (est. 1.6)	Femoral blood: Positive  Urine: 4.6  Vitreous: positive	8-Aminoclonazepam, pyrazolam (14), quinine, caffeine, ethanol (13 mg/dl)

15	<p>35 y/o male was found deceased in his room after not being seen all morning. He was last seen the night before by a roommate and was reported to have been fine with no complaints. The body was found on the floor, in full rigor with lividity, fully clothed. In his right hand was an un-capped syringe containing an unknown, light pink in color liquid substance. The roommate stated the decedent had depression and a heroin use disorder.</p>	2/15/2021	IL	<p>Iliac Blood: 5.8          Urine: 4.0          Vitreous: Pos. (est. 0.71)</p>	<p>Iliac Blood: Negative          Urine: 28          Vitreous: Positive</p>	<p>Caffeine, cotinine, mirtazapine (37)</p>
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16	<p>29 y/o female with a history of drug/alcohol use, cardiomyopathy, and Hepatitis C was found unresponsive in a vehicle outside of her boyfriend's residence. The decedent was recently released from incarceration stemming from drug charges. The decedent purchased "heroin" and "fentanyl," and the boyfriend had advised the decedent that he did not want her to bring drugs into his residence, so she remained in the vehicle. After some time, the boyfriend went to check on the decedent and she was found unresponsive. EMS was called, naloxone was administered, and cardiopulmonary resuscitation was performed. The decedent was pronounced upon arrival.</p>	2/14/2021	TN	<p>Femoral blood: 13          Urine: 10          Vitreous: pos. (est. 1.0)</p>	<p>Femoral blood: Positive          Urine: 2.1          Vitreous: positive</p>	<p>Methamphetamine (150), amphetamine (32), caffeine, cotinine, naloxone, nicotine, mirtazapine (160)</p>
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17	47 y/o male with a history of heroin use was found deceased in his bed at his residence.	2/18/2021	IA	Femoral blood (P): 5.0  Heart blood (C): 12  Urine: 2.1	Femoral blood: positive  Heart blood: negative  Urine: 0.5	Flunitazene (femoral blood: 2.1, heart blood: 4.8, urine: 0.5), 8-aminoclonazepam, flualprazolam, fentanyl (3.0), norfentanyl (0.44), 4-ANPP, delta-9 THC (0.52), delta-9 carboxy THC (12), caffeine, cotinine, nicotine, bupropion (300), hydroxybupropion (290), 10-hydroxycarbazepine (9.5 mcg/ml), quetiapine (590), gabapentin (34 mcg/ml)
18	32 y/o male was found unresponsive in an abandoned building. Numerous empty baggies of suspected "heroin" and several used syringes were recovered from the scene.	2/25/2021	IL	IVC blood: 2.5  Urine: 2.0	IVC blood: negative  Urine: negative	Flunitazene (IVC blood: 0.6, urine: positive), fentanyl (6.6), 4-ANPP, caffeine, lorazepam (24), trazodone (0.083 mcg/mL), ziprasidone (10), diphenhydramine (110), quinine, ethanol (170mg/dl)

19	<p>32 y/o male with a history of drug/alcohol use and endocarditis of the tricuspid valve with regurgitation was found unresponsive at a motel by a friend where he had been residing. EMS was called and the decedent was confirmed to be asystole on arrival. Multiple forms of drug paraphernalia, including syringes, glass pipes, a small baggie of an unspecified white powder, and naloxone were found on the scene. The nares emitted a red-tinged fluid bilaterally.</p>	1/21/2021	TN	<p>Femoral blood: 10          Urine: 28          Vitreous: pos. (est. 3.7)</p>	<p>Femoral blood: negative          Urine: 10          Vitreous: negative</p>	<p>Fentanyl (3.2), norfentanyl (1.1), 4-ANPP, methamphetamine (3900), amphetamine (160), caffeine, cotinine, quinine</p>
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20	53 y/o female with a history of heroin use was found unresponsive by family at her residence and transferred to a hospital. The decedent was diagnosed with cardiac arrest and an anoxic brain injury and admission urine was positive for amphetamines, benzodiazepines, and opiates. Brain death was ruled 5 days after admission. A burnt spoon and bag containing an illicit substance was located at the decedent's residence.	1/21/2021	TN	Blood: 1.4	Blood: Positive	Etizolam (54), <i>para</i> -fluorofentanyl (28), 4-ANPP, methadone (130), morphine (36), caffeine, naloxone, mirtazapine (52)
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## 7. Dependence Potential

### A. *Animal Studies*

In morphine-dependent rhesus monkeys, metonitazene was 100-fold more potent than morphine sulfate in suppressing the symptomology of opioid withdrawal (Aceto et al., 1992; Deneau, et al. 1959).

### B. *Human Studies*

Human studies on the ability of metonitazene to produced physiological dependence have not been conducted. However, given its pharmacological profile, metonitazene likely retains the ability to produce physiological dependence common to most opioids. Though there are no empirical studies, reports for users support this conclusion (Reddit, 2020 B).

## 8. Abuse Potential

### A. *Animal Studies*

Preclinical studies on the abuse potential of metonitazene (e.g., conditioned place preference, operant self-administration, intracranial self-stimulation) were not identified.

### B. *Human Studies*

No human abuse liability studies have been conducted. However, metonitazene can be synthesized as a free base or as a hydrochloride salt (Hunger et al., 1960). Thus, this drug could be administered by routes with faster pharmacokinetics, associated with greater abuse potential among opioids such as: smoking, insufflation, and injection. Anecdotal reports from user forums such as Reddit and Bluelight (See section 4A), and forensic evidence obtained at the scene of overdose events (i.e., the presence of injection-related paraphernalia and pipes support this conclusion (Krotulski et al., 2021).

## 9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Metonitazene has no approved therapeutic application.

## 10. Listing on the WHO Model List of Essential Medicines

Metonitazene is not listed on the WHO list of essential medicines.

## 11. Marketing Authorizations (as a Medicinal Product)

Metonitazene has no approved therapeutic applications and has never been granted a marketing authorization as a medicinal product for human or veterinary use.

## 12. Industrial Use

Metonitazene has no reported industrial uses.

## 13. Non-Medical Use, Abuse and Dependence

Population surveys and human abuse liability data could not be found. However, data from post-mortem reports suggest that because of its potency, metonitazene may be being used as an adulterant to increase the potency of heroin (in a similar manner to fentanyl (Krotulski et al., 2021). Metonitazene use did not seem to be intentional. In most cases, decedents reported purchasing heroin or fentanyl. Internet forums that cater to drug users do however suggest that there is interest in metonitazene among experienced opioid users (e.g., queries about its potency, subjective pharmacodynamic profile, etc.). Though the frequency of use could not be estimated.

#### **14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence**

Metonitazene is offered for sale by numerous internet retailers. Because drug users are likely to obtain metonitazene through unregulated sources, purity and quantity are not assured, thus presenting an additional risk of adverse reactions. Currently, metonitazene has a small impact on public health, as its presence in the drug market is minimal. However, given its pharmacodynamic profile metonitazene appears to have a high risk for recreational use, physiological dependence, and overdose.

#### **15. Licit Production, Consumption and International Trade**

Metonitazene is available for sale by pharmaceutical retailers for research and forensic applications only.

#### **16. Illicit Manufacture and Traffic and Related Information**

In March of 2019, metonitazene was identified from the testing of drug paraphernalia and seizures in Alberta Canada (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2021) and later in Ontario (KitchenerToday.com, 2021).

In Europe, the first reports of Metonitazene appear in Germany in 2020 (UNODC, 2020; European Monitoring Centre for Drugs and Drug Addiction, 2020). In the U.S., metonitazene was first reported by NPS Discovery after detection in a seized drug powder in July 2020 (Krotulski et al., 2020 A). Furthermore, the National Forensic Laboratory Information System identified 23 cases of metonitazene across U.S. federal state, and local laboratories between January 1st 2021, and March 31st 2021 (NFLIS, 2021).

Metonitazene is offered for sale by numerous internet sites, which do not appear to be reputable pharmaceutical retailers. Some are self-reported as based in China, and state that their metonitazene product can be shipped worldwide (Global B2B Marketplace, 2021).

#### **17. Current International Controls and Their Impact**

Metonitazene is not currently under international control. In response to concerns from the WHO, the U.S. Department of Health and Human Services has published a request for comments in the Federal Register concerning the abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes of several drugs, including metonitazene (U.S. Food and Drug Administration, 2021).

#### **18. Current and Past National Controls**

At the national level, metonitazene does not appear to be subject to restrictive measures within the member states of the European Union (EMCDDA, 2020). At the U.S. federal level, metonitazene is not explicitly a scheduled substance. However, the structurally related etonitazene and isotonitazene have been placed under the most restrictive controls in the U.S. (Drug Enforcement Administration, 2020). It is unclear if metonitazene is

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sufficiently similar in structure to these drugs to fall under these same scheduling restrictions as an “analog” on either drug. Some states such as Virginia, North Carolina, and Ohio have used emergency scheduling to place the drug under the most restrictive controls (lrs.sog.unc.edu., n.d.; law.lis.virginia.gov., n.d.; Pharmacy.ohio.gov, n.d).

**19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance**

No further comments.

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## Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Data were obtained from 98 Member States (12 African Region, 12 Eastern Mediterranean Region, 37 European Region, 14 Region of the Americas, 7 South-East Asia Region and 16 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire was 9 (1 African Region, 2 Eastern Mediterranean Region, 2 European Region, 2 Region of the Americas, 1 South-East Asia Region and 1 Western Pacific Region), leaving 89 countries that agreed to provide data.

Of the 89 countries who agreed to provide data, 15 countries had information on metonitazene (Table 1).

Table 1. Numbers of countries providing information on metonitazene

Region	Number of countries without information	Number of countries with information on substance
African	4	0
Eastern Mediterranean	6	0
European	20	10
Region of the Americas	9	3
South-East Asia	4	0
Western Pacific	9	2
Total (67)	52	15

### APPROVED MEDICAL, SCIENTIFIC OR INDUSTRIAL USE

One country (European) reported approved human medical products containing metonitazene being available in their country. No countries reported therapeutic indications, scientific use or industrial use relating to metonitazene.

## EPIDEMIOLOGY OF NON-MEDICAL USE

Four countries (2 European, 2 Region of the Americas) reported there was evidence from health professionals and law enforcement of non-medical use of metonitazene in their country (use outside of the medical, industrial or scientific context).

### Routes of administration and formulations

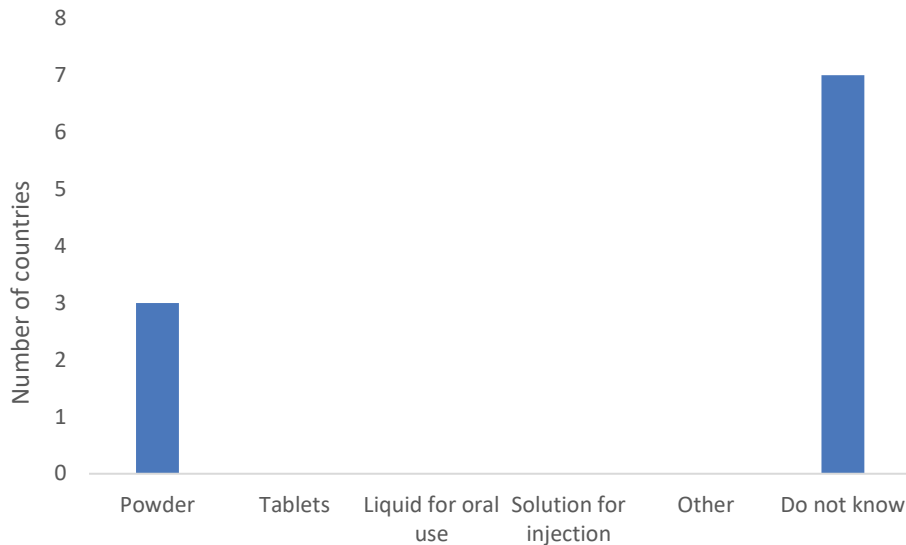
The most commonly reported administration routes for metonitazene were oral and injection (Table 2).

Table 2. Reported routes of metonitazene administration

Route of administration	Number of countries
Oral	2
Injection	2
Smoking	1
Do not know	9

The most commonly reported formulation of metonitazene was powder (Figure 1).

Figure 1. Formulations of metonitazene

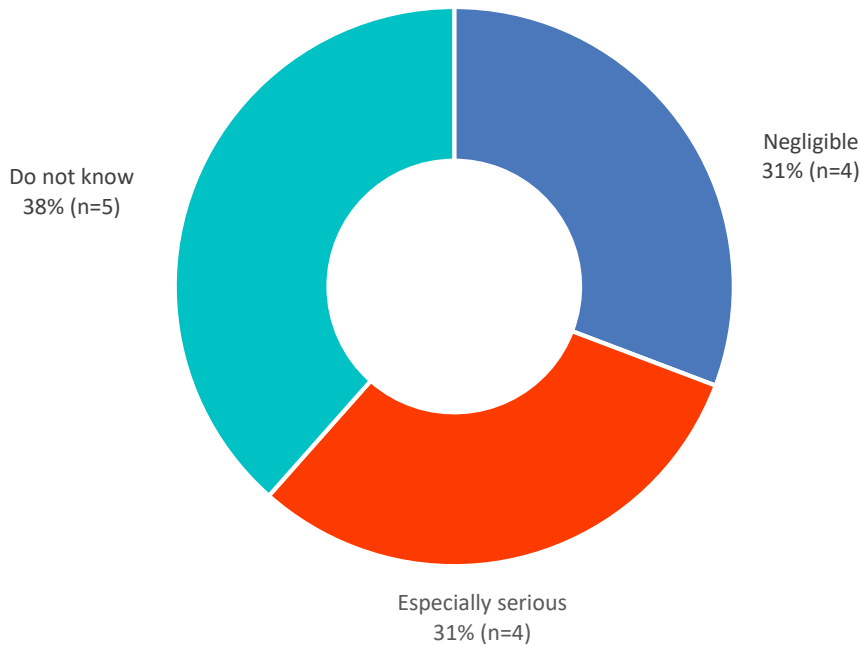


### Perceived negative health impact

Four countries (2 European, 2 Region of the Americas) reported the level of negative health impact due to metonitazene’s non-medical consumption as “especially serious” (Figure 2).

One country (Region of the Americas) reported that “metonitazene has been encountered on the illicit drug market and has been positively identified in 20 postmortem cases”. Another country (Region of the Americas) reported that “one death due to metonitazene was confirmed in a public health alert made by [a jurisdiction’s] Chief Medical Examiner”. One country (European) noted that metonitazene had been identified in the femoral blood of a fatality.

Figure 2. Countries reporting negative health impact of the non-medical consumption of metonitazene



### Emergency Department visits

No countries were aware of emergency room/department visits related to metonitazene.

### Deaths

One country (Region of the Americas) reported a death in 2019 where metonitazene was the only substance involved. Two countries (1 European, 1 Region of the Americas) reported deaths where metonitazene and other substances were involved – 20 deaths in 2021 (Region of the Americas) and 1 death in 2020 (European).

### Drug Dependence

No countries reported they were aware of people presenting to drug dependence treatment in their country due to use of metonitazene.

## CURRENT DRUG CONTROL

Nine countries (7 European, 1 Region of Americas, 1 Western Pacific) reported metonitazene is currently controlled under national legislation to regulate its availability. Table 3 shows reported activities involving metonitazene.

Table 3. Reported activities involving metonitazene for purposes other than medical, scientific or industrial use.

Activity	Number of countries
Trafficking	1
Internet sales (from abroad to buyers in respondent's country)	1
Internet sales (other or location of sellers and website unknown)	1
Other *	1
Do not know	9

\* Other metonitazene activities: "This substance has been anecdotally identified in investigations e.g. in 2018. The substance has been listed in internet markets with the involvement of known sites investigated in cases concerning other, already controlled substances"

### Seizures

Two countries (2 Region of Americas) reported seizures of metonitazene in 2021. Seizure numbers ranged from 61 to 142 (Table 4).

One country (Region of Americas) reported 105 seizures of metonitazene in 2020.

Table 4. Reported seizures of metonitazene

Year	Number of countries reporting seizures	Number of seizures
2021	2	203
2020	1	105

Thirteen countries (9 European, 2 Region of the Americas, 2 Western Pacific) reported having the forensic laboratory capacity to analyze metonitazene.