Fentanyl analogues (ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl):

Report to the Expert Advisory Committee on Drugs

Prepared by the Ministry of Health

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SUMMARY

Purpose

This paper provides an overview of three fentanyl analogues, ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl, and the options for scheduling them under the Misuse of Drugs Act 1975. Specific information prepared by the World Health Organization (WHO) on the individual substances is provided alongside this paper (Annex 1-3).

Substance

The fentanyl analogues to be considered by the Expert Advisory Committee on Drugs (the Committee) are:

- *p*-methoxy-butyrylfentanyl
- *p*-Fluoro-butyrylfentanyl
- ortho-fluorofentanyl.

Fentanyl analogues are synthetic opioids that most commonly cause sedative and analgesic effects. Fentanyl itself is a synthetic opioid analgesic, and is a powerful painkiller with a higher potency and faster onset than other opioids.

Why they are being considered

There has been a significant number of deaths and harm associated with the use of fentanyl analogues internationally. Ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl are being considered above other fentanyl analogues as they have been recently reviewed by the Expert Committee on Drug Dependence (ECDD) and scheduled under UN conventions. The ECDD considered these three analogues due to their appearance in assays of blood samples from people experiencing acute opioid overdose and implication in multiple deaths around the world.

Both *p*-fluoro-butyrlfentanyl and ortho-fluorofentanyl have been scheduled in the United Nations Single Convention on Narcotic Drugs of 1961, of which New Zealand is a signatory. The fentanyl analogues presented must therefore be considered for scheduling in NZ to meet our international obligations for the control of this substance. *P-Methoxy-butyrfentanyl* was placed under watch by the WHO Secretariat due to the limited evidence of significant public health impacts.

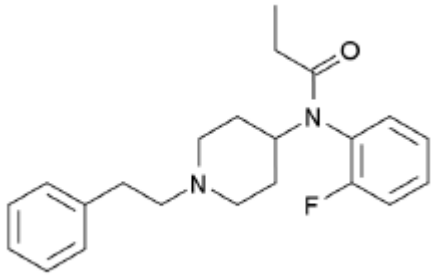
1.0 SUBSTANCE IDENTIFICATION AND CHEMISTRY

1.1 Identification

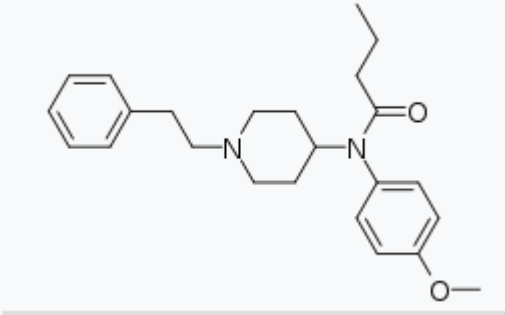
Ortho-fluorofentanyl

IUPAC name: *N*-(2-Fluorophenyl)-*N*-[1-(2-phenylethyl)-4-piperidinyl]-propanamide

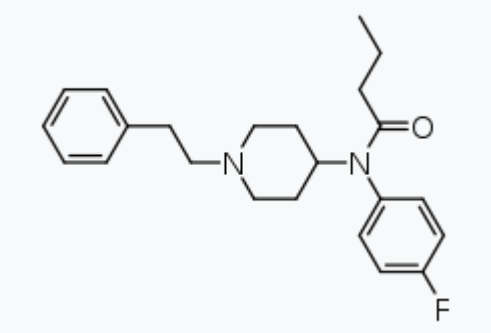
CAS number: 910616-29-4
Molecular weight: 354.5 g mol^{-1}
Molecular formula: $C_{22}H_{27}FN_2O$
Appearance: White crystalline powder
Solubility: Unknown



p-methoxy-butyrfentanyl
IUPAC name: *N*-(4-methoxyphenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide
CAS number: 2088842-68-4
Molecular weight: 380.5 g mol^{-1}
Molecular formula: $C_{24}H_{32}N_2O_2$
Appearance: White powder/neat solid
Solubility: Unknown



p-fluoro-butyrfentanyl
IUPAC name: N-(4-Fluorophenyl)-N-(1-phenethylpiperidin-4-yl)butyramide
CAS number: 244195-31-1
Molecular weight: 368.5 g mol^{-1}
Molecular formula: $C_{23}H_{29}FN_2O$
Appearance: Off-white powder/neat crystalline solid
Solubility: Unknown

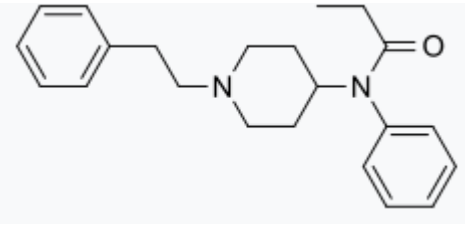


1.2 Therapeutic Value

There are no known therapeutic uses for ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl or *p*-fluoro-butyrfentanyl.

1.3 Similarity to Other Known Substances

All three substances are synthetic analogues of fentanyl, which is a class B controlled drug under the Misuse of Drugs Act. The structure of fentanyl is shown below. The three analogues differ from the core fentanyl structure through simple substitutions.



Fentanyl and fentanyl analogues are part of the opioid group of substances. The specific effects of these substances are discussed in section 2.2 – Specific Effects, of this report.

1.4 Methods of Manufacturing

Manufacturing information can be found in section 2D of the attached WHO reports.

2.0 RISK OF HARM IN NEW ZEALAND

2.1 Likelihood or Evidence of Abuse

The previous EACD paper on methoxyacetylfentanyl and cyclopropylfentanyl discussed the trends of opioid abuse internationally and in New Zealand (Annex 4, page 7). There is no evidence that ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl specifically are being abused in New Zealand. Additionally, there have not been any border seizures by NZ Customs Service. However, international experience suggests there is likely to be abuse potential for the three substances, especially among experimental drug users.

Internationally, the United Nations Office on Drugs and Crime (UNODC) provides information to registered users on trend data of New Psychoactive Substances. Both monitoring systems rely on self-reported data and are likely to provide an incomplete picture, however, are a useful indicator for emerging issues.

Table 2: Notifications to the UNODC Early Warning Advisory on New Psychoactive Substances.

	UNODC reports	First notified	Number of nations
p-Methoxy-butyrylfentanyl	4	2015	3
p-Fluoro-butyrylfentanyl	13	2015	9
Ortho-fluorofentanyl	7	2016	6

2.2 Specific Effects

The effects of ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl in humans are primarily known from reports of fatalities. Specific information is very limited as there have been no clinical studies on the substances. Because of the structural similarity to fentanyl, their effects are expected to be similar.

Specific effects of fentanyl include:

- analgesia
- decreased gastrointestinal motility
- respiratory depression
- drowsiness
- changes in mood
- alterations of the endocrine and autonomic nervous systems.

Adverse effects include:

- apnoea
- circulatory depression
- respiratory arrest
- shock
- cardiac arrest.

2.2.1 Toxicology

Toxicology information specific to each of ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl can be found in section 5 of the attached WHO reports.

2.2.2 Pharmacology

Like pethidine, morphine, and other opioid drugs, fentanyl analogues work by binding to the body's opioid receptors, which are found in areas of the brain that control pain and emotions. When opioid drugs bind to these receptors, they can drive up

dopamine levels in the brain's reward areas, producing a state of euphoria and relaxation. The μ-opioid receptor mediates analgesic and addictive properties of substances that activate this receptor (Metthes et al. 1996). Fentanyl analogues vary in potency and dosage required to produce desired effects but generally have a high affinity for the μ-opioid receptor. Table 3 provides an overview of the relative potencies of ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl, morphine and fentanyl, based on ED_{50}[1] values of each substance. Potencies relative to morphine and fentanyl have been included only where they were assayed alongside the fentanyl analogue being analysed. The information in Table 3 is intended only as a guide to potencies, as assays are highly variable and are of limited value when compared to each other.

Pharmacology information specific to each of ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl can be found in section 5 of the attached WHO reports.

Note that no pharmacokinetic or pharmacodynamic studies of ortho-fluorofentanyl are reported in the preclinical or clinical scientific literature. It first appeared in toxicological assays in the USA in 2016. There are case reports of two hospitalisations as well as one death from using this drug. Serum samples from one of the hospitalised patients and a blood sample from the deceased contained ortho-fluorofentanyl in concentrations of 2.5 and 2.4 ng/mL, respectively (Helland et al. 2017).

Table 3: Analgesic Potencies of Synthetic Opioids in Mice

	Assay Method	ED_{50}† Dose	Potency Relative to	
			Morphine	Fentanyl
Morphine	Hot-plate	2.54mg/kg^	1	1/100≠
Fentanyl	Hot-plate	0.05mg/kg^	100≠	1
p-Methoxy-butyrylfentanyl	[35S]GTPγS	0.1057mg/kg≠	74≠	1≠
p-Fluoro-butyrylfentanyl	[35S]GTPγS	0.9081mg/kg≠	8.6≠	1/12≠
Ortho-fluorofentanyl	N/A	N/A	N/A	N/A

† ED_{50} – The dose that produces a specific effect in 50% of the sample population
≠ - WHO Critical Review Report (substance specific)
^ - Dykstra et al 2011
N/A – No data available

[1] The dose that produces a specific effect in 50% of the sample population

2.3 Risks to Public Health

As these substances have not been identified in New Zealand, no specific risk can be attributed to them. The public health risks of fentanyl analogues as a group have been reviewed in a previous EACD paper (Annex 4, page 10). Section 14 of the ECDD reports reviews the public health risk of ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl or *p*-fluoro-butyrfentanyl in the international context.

2.4 Potential to Cause Death

There have been no reported deaths in New Zealand due to any of ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl or *p*-fluoro-butyrfentanyl. Section 6 of the ECDD reports discusses reports of fatalities associated with ortho-fluorofentanyl and *p*-fluoro-butyrfentanyl. There is limited evidence of a causal relationship between *p*-methoxybutyrfentanyl and death as no fatal reports have been identified. Due to their similarity to fentanyl, it is reasonable to assume that ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl carry a similar potential to cause death.

As a group, fentanyl analogues are known to carry a significant potential to cause death. Varying fentanyl analogues were present in 720 opioid overdose deaths in ten USA states between July and December 2016 alone, (O'Donnell et al. 2017). A literature review of deaths associated in fentanyl and fentanyl analogues found that the majority of deaths are associated with pulmonary oedema and congestion, as well as aspiration of gastric contents (Giorgetti et al., 2017). Additionally, the majority of overdoses from fentanyl analogues assessed in the USA were associated with concurrent use of other illicit drugs (O'Donnell et al. 2017).

It is generally considered that the most serious acute health risk from using fentanyl analogues is likely to be rapid and severe respiratory depression, which in overdose could cause apnoea[1], respiratory arrest, and death (EMCDDA, 2017). Factors which may influence or exacerbate this risk include:

- difficulty in accurately diluting a fentanyl analogue
- using different routes of administration with higher bioavailability
- concurrent use of other central nervous system depressants such as alcohol or benzodiazepines (O'Donnell et al. 2017)
- no or limited opioid tolerance
- using the substances alone at home.

Overdoses can be effectively reversed by naloxone, a μ-opioid receptor antagonist.

[1] *Apnoea* –a temporary cessation of breathing.

2.5 Physical or Psychological Dependence

Information on the potential for dependence of ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl can be found in the attached WHO reports in sections 7 and 8.

3.0 CLASSIFICATION

3.1 Classification and Regulation in New Zealand

Currently the fentanyl analogues being considered in this paper are not specifically scheduled in the Misuse of Drugs Act, but can be captured under one of three pathways:

- Section 2 definition of controlled drug analogue as having a structure substantially similar to any controlled drug or
- Schedule 3 part 7 as a **controlled drug analogue** of fentanyl or
- Schedule 2 part 3 as an isomer, ester, ether or salt of fentanyl or another scheduled fentanyl analogue.

In our opinion, *p*-methoxy-butyrylfentanyl and *p*-fluoro-butyrfentanyl meet the examples set in Schedule 3 part 7. We therefore consider these class C7 controlled drugs, as analogues of fentanyl.

In our opinion, ortho-fluorofentanyl is considered an isomer of the class B3 controlled drug, *p*-fluorofentanyl, and therefore also captured as a class B3 controlled drug.

We are currently awaiting confirmation from ESR for these classifications.

The current penalties for these classifications are shown in table 5.

3.2 International Classification

Australia

Several fentanyl analogues are in Schedule 9 of the Poisons Standard (SUSMP), however, none of those being considered by the EACD are specifically scheduled. It is possible they could be captured as a derivative of fentanyl or another scheduled substance as per Part 1 subsection 1(2) of the Poisons Standard.

United States of America

Ortho-fluorofentanyl, *p*-fluoro-butyrylfentanyl, and *p*-methoxy-butyrylfentanyl are Schedule I Controlled Substances under the Controlled Substances Act.

Canada

Fentanyl's, their salts, derivatives, and analogues and salts of derivatives and analogues are in Schedule I of the Controlled Drugs and Substances Act. It is likely

that ortho-fluorofentanyl, *p*-fluoro-butyrylfentanyl, and *p*-methoxy-butyrylfentanyl would be captured by this entry.

United Kingdom

Fentanyl is scheduled under Schedule 2 Part I Class A, which includes any stereo isomeric form, any salt, ester or ether of these substances under the Misuse of Drugs Act 1971.

3.3 UN Classification

P-fluoro-butyrfentanyl and ortho-fluorofentanyl have been placed in Schedule I of the UN Single Convention on Narcotic Drugs 1961. *P-methoxy-butyrfentanyl* has been placed under surveillance by the WHO ECDD.

4.0 OTHER RELEVANT INFORMATION

4.1 Origin and History

Fentanyl analogues have been developed since fentanyl was first discovered in the 1960s. Ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl have been identified as part of a new wave of fentanyl analogues that started entering illicit markets from 2014.

The UNODC Early Warning Advisory (EWA) on New Psychoactive Substances (NPS) and EMCDDA were set up to monitor the emergence of NPS in member states. The reports to the EWA on ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl are summarised in Section 2.1, Table 2 of this report.

4.2 Anticipated Future Trends

Fentanyl analogues

The rapid rise in harms related with fentanyl analogues seen in Europe and North America may become evident in New Zealand. As the distribution of fentanyl analogues is highly profitable, overseas drug traffickers may target the New Zealand drug market.

International trends show the adulteration of counterfeit pharmaceuticals with fentanyl analogues. There is potential for counterfeit pharmaceuticals adulterated with fentanyl analogues to be imported and enter the New Zealand drug market, following international trends. However, there is no specific evidence of this occurring at this time.

Australia has experienced a high number of opioid overdose deaths in recent years. There were 498 fentanyl related deaths which occurred between 2010 and 2015, which represents a 1,800 percent rise from the previous decade (Australian Bureau of Statistics 2016). There is one confirmed report of a death from acetylfentanyl in Australia (Moss et al. 2017), which may indicate issues with analogues are emerging

in Australia similar to North America and Europe. New Zealand may be susceptible to these trends.

Ortho-fluorofentanyl, p-methoxy-butyrfentanyl and p-fluoro-butyrfentanyl

As these substances have not been seen in New Zealand, it is difficult to predict their trend in our markets. However, considering the trends of these substances overseas, it is reasonable to predict a risk of these, and other fentanyl analogues, may pose a significant public health risk in the future.

4.3 Presumption of supply

Presumption of supply for fentanyl analogues has been previously discussed at the September 2018 EACD meeting (Annex 5). Table 4 provides information specific to ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl. It is recommended that the approach to setting a presumption for supply should be consistent between all fentanyl analogues.

Table 4**:** Anecdotal Dose size and possible amounts for presumption of supply for ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and *p*-fluoro-butyrfentanyl

Typical Dose	**Light**	**Common**	**Strong**
p-Methoxy-butyrylfentanyl	1 mg	2 – 5 mg	7 mg
p-Fluoro-butyrylfentanyl	300 µg	600 - 900 µg	900 - 1200 µg
p-fluorofentanyl≠	10 – 25 µg	25 - 40 µg	40 – 65 µg
Median	**0.43 – 0.44 mg**	**0.875 – 1.98 mg**	**2.6 – 2.76 mg**
*Median less potent**	**0.155 – 0.1625 mg**	**0.31 – 0.47 mg**	**0.47 - 0.63 mg**
Number of Doses at:	**Light**	**Common**	**Strong**
Default level (56 g)			
p-methoxy-butyrylfentanyl	56,000	11200 - 28000	8,000
p-fluoro-butyrylfentanyl	186,667	62,222 - 93,333	46,667 - 62,222
p-fluorofentanyl≠	2,240,000 - 5,600,000	1,400,000 - 2,240,000	861,538 - 1,400,000
Median	**872,556 – 1,947,556**	**491,141 – 787,111**	**305,402 - 490074**
*Median less potent**	**1,213,334 – 2,893,333**	**731,111 – 1,166,667**	**454,103 – 731,111**

Amount for:	**Light**	**Common**	**Strong**
25 doses			
p-methoxy-butyrylfentanyl	0.025 g	0.05 - 0.125 g	0.175 g
p-fluoro-butyrylfentanyl	0.0075 g	0.015 – 0.0225 g	0.0225 – 0.03 g
p-fluorofentanyl≠	0.00025 – 0.000625g	0.000625 – 0.001 g	0.001 – 0.001625 g
Median	**0.00034 – 0.011 g**	**0.0219 – 0.0495 g**	**0.066 – 0.069 g**
*Median less potent**	**0.003875 – 0.00041 g**	**0.0078 – 0.01175 g**	**0.01175 – 0.0158 g**

	Light	**Common**	**Strong**
100 doses			
p-methoxy-butyrylfentanyl	0.1 g	0.2 – 0.5 g	0.7 g
p-fluoro-butyrylfentanyl	0.03 g	0.06 – 0.09 g	0.09 - 0.12 g
p-fluorofentanyl≠	0.001 – 0.0025 g	0.0025 - 0.0040 g	0.0040 – 0.0065 g
Median	**0.044 g**	**0.0875 – 0.198 g**	**0.28 g**
*Median less potent**	**0.0155 – 0.01625 g**	**0.03125 – 0.047 g**	**0.047 – 0.063 g**

* Less potent – *p*-Fluoro-butyrylfentanyl and *p*-fluorofentanyl.
≠ - No information is available as to the typical dosing for ortho-fluorofentanyl. Dosages in this table are for *p*-fluorofentanyl.

5.0 CLASSIFICATION OPTIONS

Although the fentanyl analogues are being considered together, if the Committee considers that they have different risks of harm, different scheduling recommendations can be applied to each substance considered.

If a presumption of supply is to be set, it is recommended that it is set at half a gram, or 25 flakes, tablets, capsules, or other drug forms, each containing some quantity of the drug. The Committee can also recommend different levels for each substance, or allow the default of 56 grams to apply.

Option 1: **Status Quo. Decline to specifically schedule ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and/or *p*-fluoro-butyrfentanyl under The Misuse of Drugs Act.**

Currently, ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and/or *p*-fluoro-butyrfentanyl are all likely to be captured by the Misuse of Drugs Act as controlled drug analogues or an isomer of a controlled drug. If the status quo option is recommended, the specified fentanyl analogues will continue to be captured as controlled drug analogues under the Misuse of Drugs Act. Penalties (listed in Table 5 below) for

the misuse of these fentanyl analogues will be in line with substances that have a moderate risk of harm.

Control under Schedule 3 of the Misuse of Drugs Act will mean that New Zealand will not comply with some obligations under the United Nations Conventions on Narcotic Drugs 1961.

Option 2: Schedule ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and/or *p*-fluoro-butyrfentanyl as Class A controlled drugs under the Misuse of Drugs Act 1975

Substances posing a very high risk of harm to individuals or society that are highly addictive and liable to abuse, or are easily convertible into drugs that are similarly addictive and liable to abuse. These substances generally have very little to no therapeutic value.

If the Committee considers that ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and/or *p*-fluoro-butyrfentanyl have a very high risk of harm, they can recommend scheduling in Schedule 1 as Class A controlled drugs.

Control under Schedule 1 of the Misuse of Drugs Act will mean that New Zealand will comply with their obligations under the United Nations Conventions on Narcotic Drugs 1961.

Scheduling these three fentanyl analogues as Class A controlled drugs is in line with previous recommendations (such as butyrfentanyl and acetylfentanyl).

Option 3: Schedule ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and/or *p*-fluoro-butyrfentanyl as Class B controlled drugs under the Misuse of Drugs Act 1975

Substances posing a high risk of harm to individuals or society that can be highly addictive and liable to abuse, or are easily convertible into drugs that are similarly addictive and liable to abuse. These substances can have little to moderate therapeutic use.

If the Committee considers that ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and/or *p*-fluoro-butyrfentanyl have a high risk of harm they can recommend scheduling them in Schedule 2 as Class B controlled drugs. Schedule 2 has three parts. For a full breakdown of the differences in control between these parts of Schedule 2, please see the EACD Guidelines.

Control under Schedule 2 of the Misuse of Drugs Act will mean that New Zealand will comply with their obligations under the United Nations Conventions on Narcotic Drugs 1961.

Option 4: Schedule ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and/or *p*-fluoro-butyrfentanyl as Class C controlled drugs under the Misuse of Drugs Act 1975

Substances posing a moderate risk of harm to individuals or society and a moderate to high risk of abuse and dependency, or are easily convertible into drugs that are similarly addictive and liable to abuse. These substances can have little to great therapeautic use.

If the Committee considers that ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and/or *p*-fluoro-butyrfentanyl have a moderate risk of harm they can recommend scheduling them in Schedule 3 as a Class C controlled drug.

Schedule 3 has seven parts. For a full breakdown of the differences in control between these parts of Schedule 3, please see the EACD Guidelines.

The fentanyl analogues would currently be treated as Class C and C7 controlled drugs and penalties under the Misuse of Drugs Act would remain the same if they are to be scheduled as Class C controlled drugs.

Depending on which part of Schedule 3 the Committee decides to control these substances, New Zealand will not comply with some of their obligations under the United Nations Conventions on Narcotic Drugs 1961.

Table 5: Penalties under the Misuse of Drugs Act 1975

	Schedule 1 Class A Drugs	**Schedule 2 Class B Drugs**	**Schedule 3 Class C Drugs**	**Psychoactive Substances Act**
Importation, manufacture, or supply	Life imprisonment (subject to presumption of supply)	Up to 14 years imprisonment (subject to presumption of supply)	Up to 8 years imprisonment	Up to 2 years imprisonment (for individuals) or a fine not exceeding $500,00 (for a body corporate)
Conspiracy to commit an offence	Up to 14 Years imprisonment	Up to 10 years imprisonment	Up to 7 years imprisonment	N/A
Possession	Up to 6 months imprisonment or $1,000 fine or both	Up to 3 months imprisonment or $500 fine or both	Up to 3 months imprisonment or $500 fine or both	A fine not exceeding $500

6.0 FUTURE ACTIONS

If the Committee recommends that ortho-fluorofentanyl, *p*-methoxy-butyrfentanyl and/or *p*-fluoro-butyrfentanyl should be scheduled under The Misuse of Drugs Act, the Secretariat will draft a letter from the Committee to the Minister of Health to progress the advice. The Secretariat may undertake targeted consultation with industry to ensure impacts on legitimate uses is reasonable and minimised. If the status quo is recommended, the Secretariat will draft a letter from the Committee to the Minister of Health to inform him of the advice and no further action would be required.

7.0 REFERENCES

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