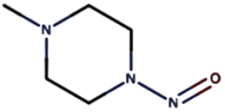
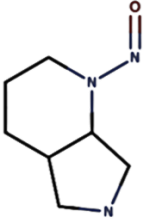
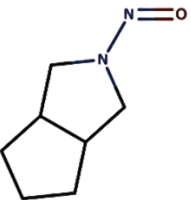
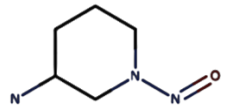
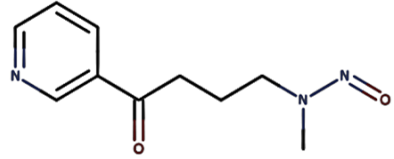
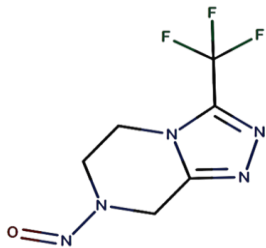
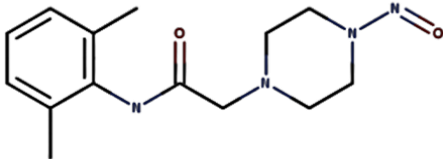
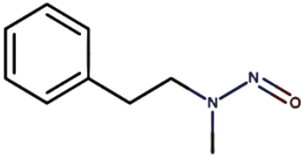
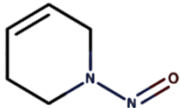
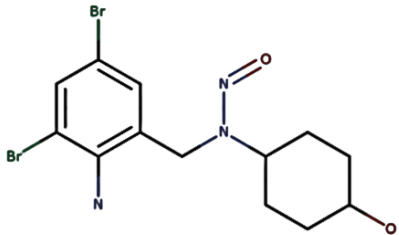


Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

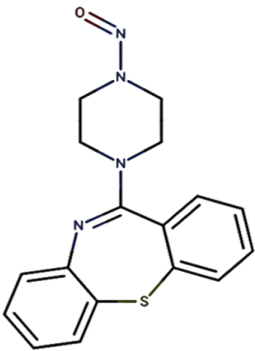
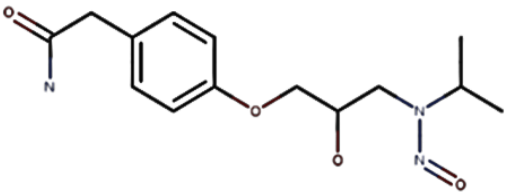
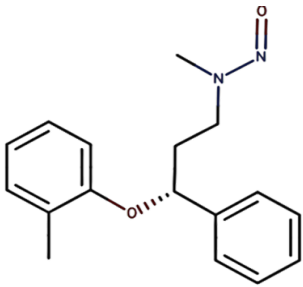
The acceptable intakes (AI) below are recommended by the Health Sciences Authority and are determined using the Carcinogenic Potency Categorization Approach (CPCA) where applicable. The source refers to drug substances that may potentially contain the nitrosamine impurity. However, this does not mean that the impurity will be found in all products or pharmaceutical forms containing the named drug substance. This list and the source examples provided are not exhaustive and will be updated as more information becomes available.

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	1-methyl-4-nitrosopiperazine	Multiple sources	3	400
	1-nitroso-pyrroloperidine	Multiple sources	4	1500
	2-nitroso-octahydrocyclopenta(c)pyrrole	Gliclazide	-	1700
	3-amino-N-nitrosopiperidine	Alogliptin	3	400
	4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone	Multiple sources	-	100

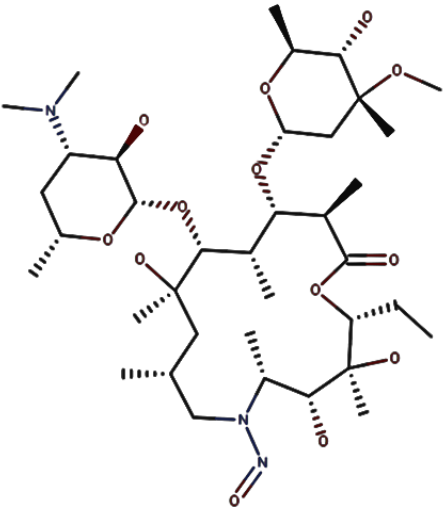
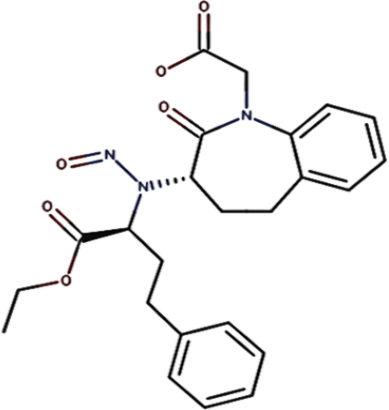
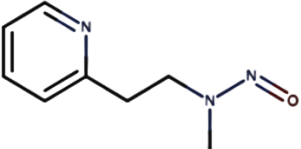
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3-a]pyrazine	Sitagliptin	-	37
	N-(2,6-dimethylphenyl)-2-(4-nitrosopiperazin-1-yl)acetamide	Ranolazine	3	400
	N-methyl-N-nitroso-phenethylamine	Multiple sources	-	8
	N-nitroso-1,2,3,6-tetrahydropyridine	Multiple sources	-	37
	N-nitroso-ambroxol	Ambroxol	-	1500

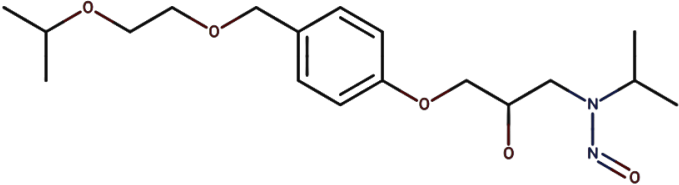
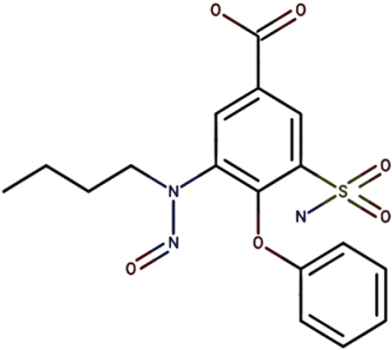
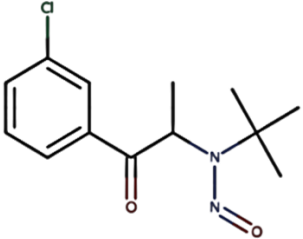
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
 <p>The structure shows a piperazine ring with an N-nitroso group (-N=O) attached to one of the nitrogen atoms. The other nitrogen atom of the piperazine ring is connected to a benzothiazine core, which consists of a benzene ring fused to a six-membered ring containing a sulfur atom and a nitrogen atom.</p>	N-nitroso-aryl piperazine / N-nitroso-desalkylquetiapine / N-nitroso-norquetiapine	Quetiapine	3	400
 <p>The structure features a benzene ring with a nitroacetamide group (-CH2-C(=O)-NH2) at the para position and an ether linkage (-O-) at the other para position. The ether oxygen is connected to a propanoic acid chain that has an isopropylamino group (-NH-CH(CH3)2) at the end. The nitrogen atom of the isopropylamino group is nitrosated (-N=O).</p>	N-nitroso-atenolol	Atenolol	4	1500
 <p>The structure shows a benzene ring with a methyl group at the para position and an ether linkage (-O-) at the other para position. The ether oxygen is connected to a propyl chain that has a nitrosated secondary amine group (-NH(CH3)-) at the end. The nitrogen atom of the secondary amine group is nitrosated (-N=O).</p>	N-nitroso-atomoxetine	Atomoxetine	-	100

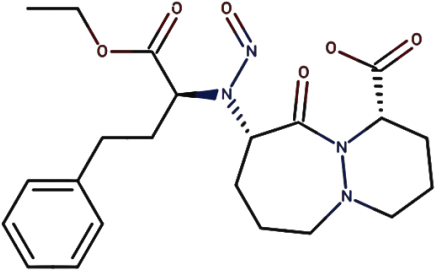
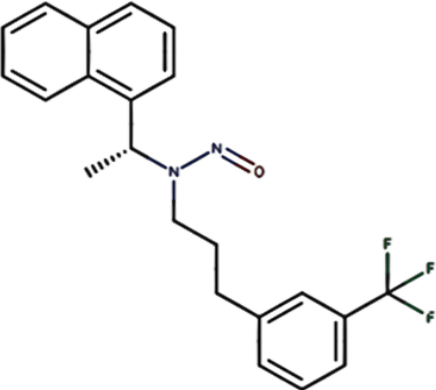
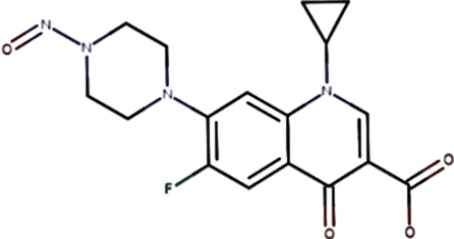
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-azaerythromycin	Azithromycin	-	Can be controlled according to ICH Q3A/B
	N-nitroso-benazepril	Benazepril	5	1500
	N-nitroso-betahistine	Betahistine	1	18

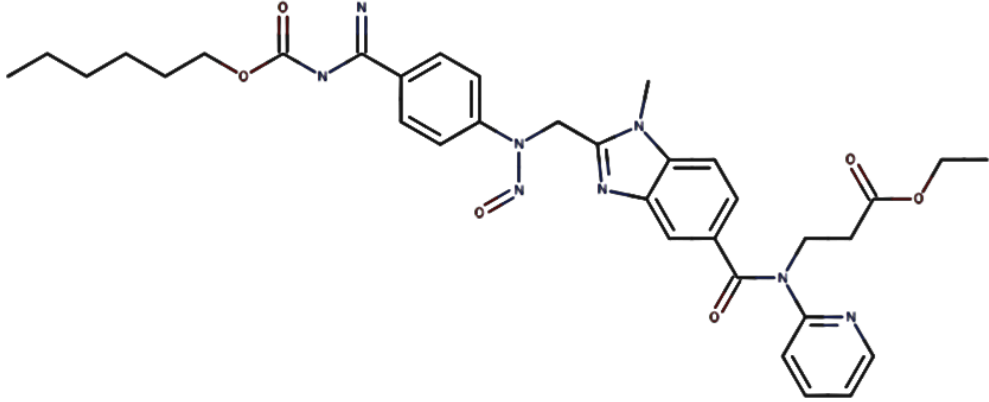
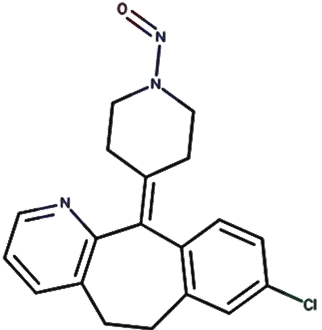
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

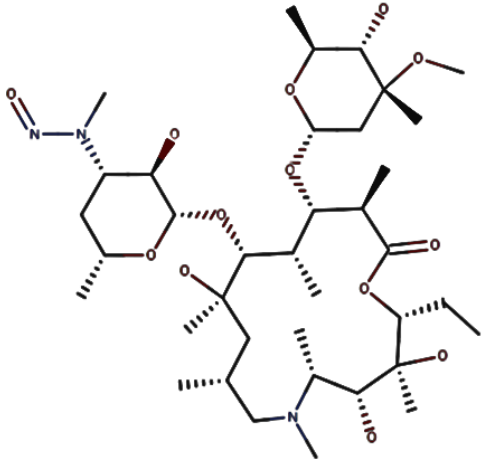
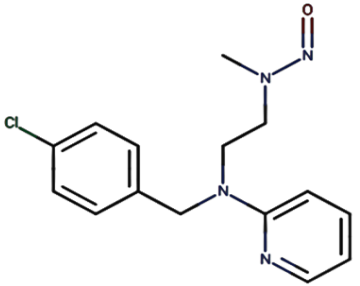
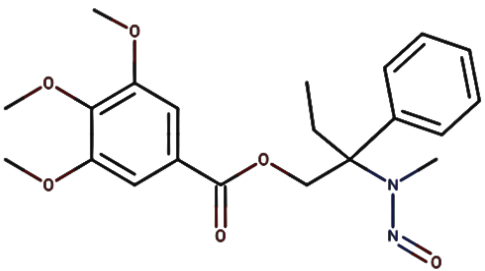
Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
 <chem>CC(C)N(N=O)CC(=O)OCCc1ccc(OCCOC(C)C)cc1</chem>	N-nitroso-bisoprolol	Bisoprolol	4	1500
 <chem>CCCCN(N=O)c1cc(C(=O)O)cc(S(=O)(=O)N)c1Oc2ccccc2</chem>	N-nitroso-bumetanide	Bumetanide	4	1500
 <chem>CC(C)N(N=O)C(=O)c1ccc(Cl)cc1</chem>	N-nitroso-bupropion	Bupropion	5	1500

Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

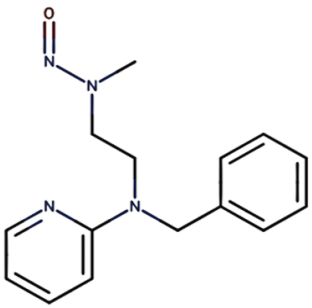
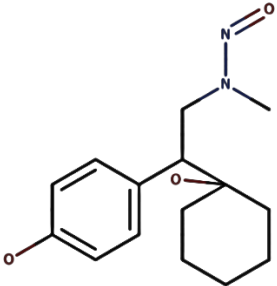
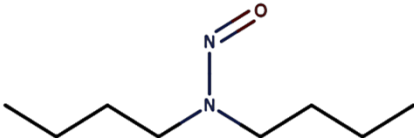
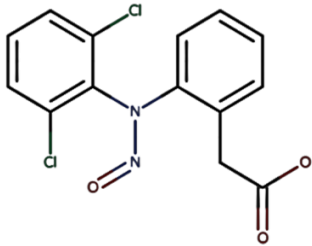
Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
 <p>The structure shows a complex molecule with a benzene ring, a propyl chain, a carbonyl group, and a bicyclic system (7-membered and 6-membered rings) with a nitroso group attached to a nitrogen atom.</p>	N-nitroso-cilazapril	Cilazapril	5	1500
 <p>The structure features a naphthalene ring system connected to a chiral center, which is further linked to a chain containing a nitroso group and a trifluoromethyl group.</p>	N-nitroso-cinacalcet	Cinacalcet	3	400
 <p>The structure is a quinolone derivative with a piperazine ring, a cyclopropyl group, a fluorine atom, and a carboxylic acid group.</p>	N-nitroso-ciprofloxacin	Ciprofloxacin	4	1500

Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

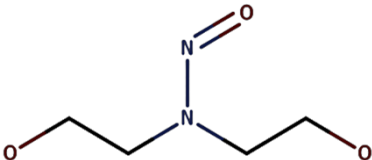
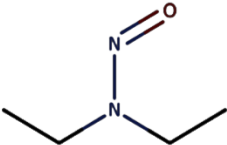
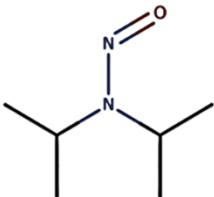
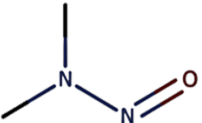
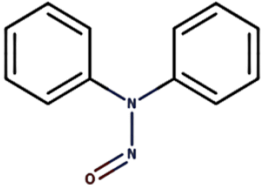
Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
 <p>The chemical structure of N-nitroso-dabigatran etexilate consists of a central benzimidazole ring system. One nitrogen of the benzimidazole is methylated. The 2-position of the benzimidazole is substituted with a 4-(N-nitroso-N-(7-oxabicyclo[2.2.1]hept-2-yl)propyl)phenyl group. The 5-position of the benzimidazole is substituted with a 2-(2-(2-(2-ethoxyacetyl)ethyl)ethyl)pyridin-5-yl group.</p>	N-nitroso-dabigatran etexilate	Dabigatran etexilate	3	400
 <p>The chemical structure of N-nitroso-desloratadine features a central bicyclic core consisting of a benzene ring fused to a seven-membered ring, which is further fused to a pyridine ring. A chlorine atom is attached to the benzene ring. A piperidine ring is attached to the seven-membered ring via a double bond, and the nitrogen of the piperidine ring is substituted with a nitroso group.</p>	N-nitroso-desloratadine	Desloratadine	3	400

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
 <p>The structure shows a complex macrolide ring system with a nitrosamine group (-N=O) attached to a methyl group on the side chain.</p>	N-nitroso-desmethyl-azithromycin	Azithromycin	-	Can be controlled according to ICH Q3A/B
 <p>The structure features a central nitrogen atom bonded to a 4-chlorophenylmethyl group, a pyridine ring, and a nitrosamine group (-N=O).</p>	N-nitroso-desmethyl-chloropyramine	Chloropyramine	1	18
 <p>The structure shows a central carbon atom bonded to a phenyl ring, an ethyl group, a methyl group, and a nitrosamine group (-N=O). This central carbon is also connected via an ester linkage to a 3,4,5-trimethoxyphenyl group.</p>	N-nitroso-desmethyl-trimebutine	Trimebutine	5	1500

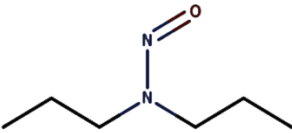
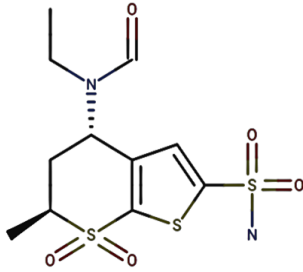
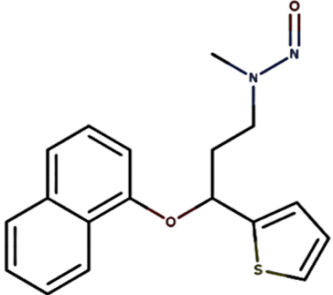
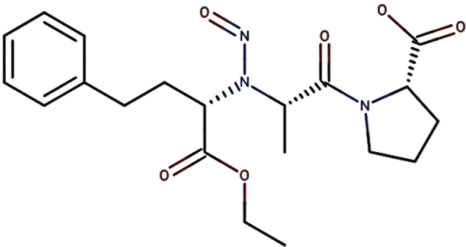
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
 <p>The structure shows a central nitrogen atom bonded to a methyl group, a nitroso group (N=O), and a propyl chain. The propyl chain is further attached to another nitrogen atom, which is bonded to a pyridine ring and a benzyl group.</p>	N-nitroso-desmethyl-tripelennamine	Tripelennamine	1	18
 <p>The structure features a central carbon atom bonded to a cyclohexane ring, a 4-chlorophenyl ring, and a propyl chain. The propyl chain is terminated by a dimethylamino group (N(CH3)2) which is nitrosated (N=O).</p>	N-nitroso-desvenlafaxine	Desvenlafaxine	1	18
 <p>The structure shows a central nitrogen atom bonded to two butyl groups and a nitroso group (N=O).</p>	N-nitroso-di-butylamine	Multiple sources	-	26.5
 <p>The structure consists of a central nitrogen atom bonded to a nitroso group (N=O), a 2,6-dichlorophenyl ring, and a propyl chain. The propyl chain is attached to a benzene ring which also has a propionic acid side chain.</p>	N-nitroso-diclofenac	Diclofenac	5	1500

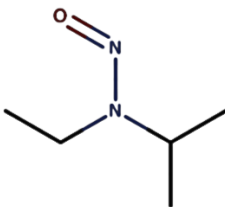
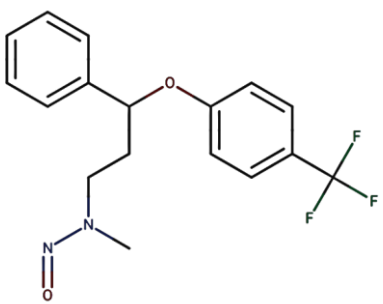
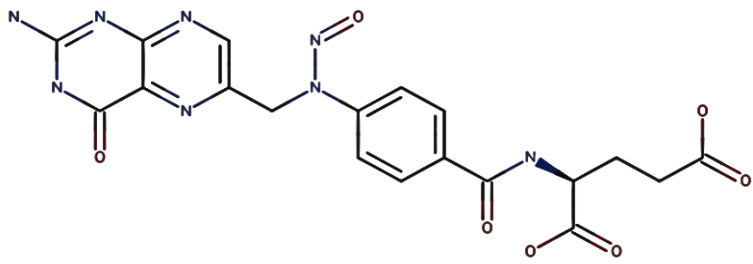
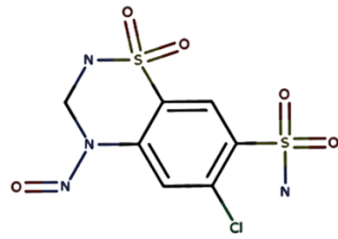
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-diethanolamine	Multiple sources	-	1900
	N-nitroso-diethylamine	Multiple sources	-	26.5
	N-nitroso-diisopropylamine	Multiple sources	-	26.5
	N-nitroso-dimethylamine	Multiple sources	-	96
	N-nitroso-diphenylamine	Multiple sources	-	78000

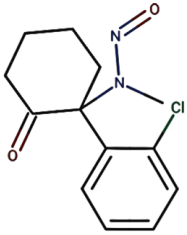
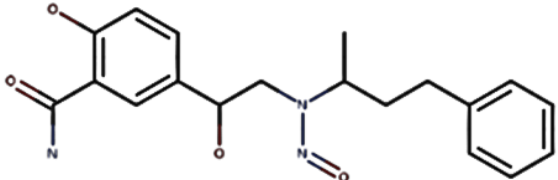
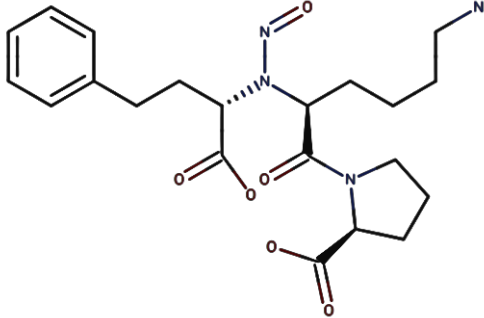
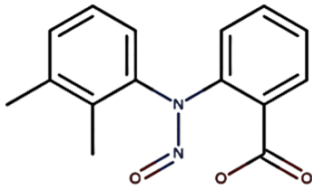
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-dipropylamine	Multiple sources	-	26.5
	N-nitroso-dorzolamide	Dorzolamide	2	100
	N-nitroso-duloxetine	Duloxetine	-	100
	N-nitroso-enalapril	Enalapril	5	1500

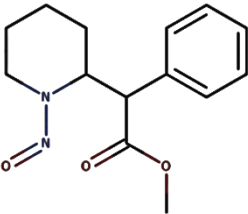
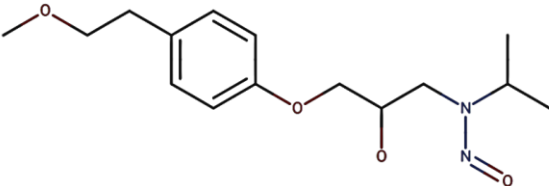
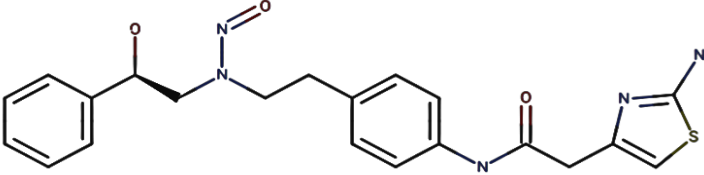
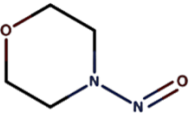
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-ethylisopropylamine	Multiple sources	-	26.5
	N-nitroso-fluoxetine	Fluoxetine	-	100
	N-nitroso-folic acid	Folic acid	4	1500
	N-nitroso-hydrochlorothiazide	Hydrochlorothiazide	-	Can be controlled according to ICH Q3A/B

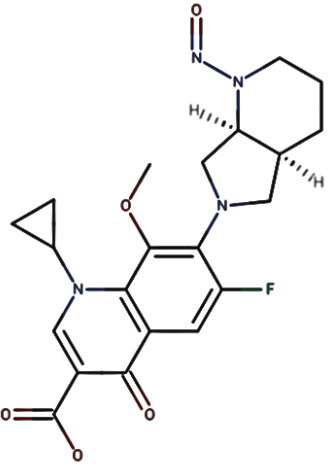
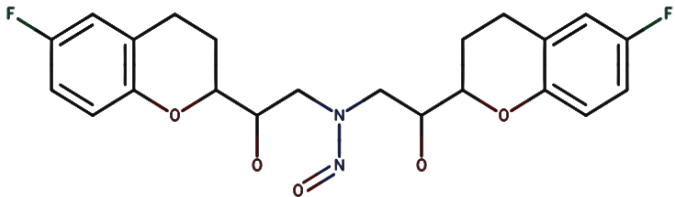
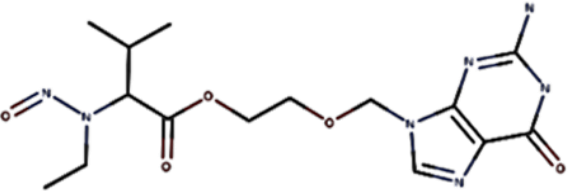
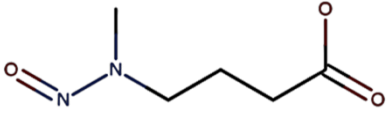
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
 <p>The structure shows a bicyclic ketamine core with a nitroso group (-NO) attached to the nitrogen atom and a chlorine atom on the adjacent carbon.</p>	N-nitroso-ketamine	Ketamine	5	1500
 <p>The structure shows a labetalol molecule with a nitroso group (-NO) attached to the nitrogen atom of the secondary amine.</p>	N-nitroso-labetalol	Labetalol	4	1500
 <p>The structure shows the complex structure of lisinopril with a nitroso group (-NO) attached to the nitrogen atom of the secondary amine.</p>	N-nitroso-lisinopril	Lisinopril	5	1500
 <p>The structure shows mefenamic acid with a nitroso group (-NO) attached to the nitrogen atom of the secondary amine.</p>	N-nitroso-mefenamic acid	Mefenamic acid	-	78000

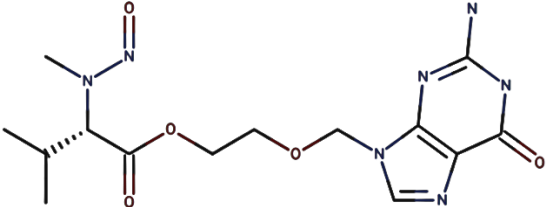
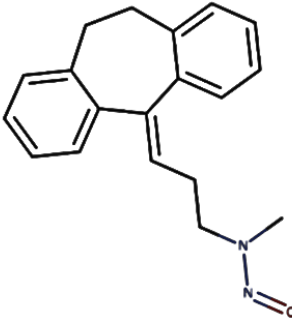
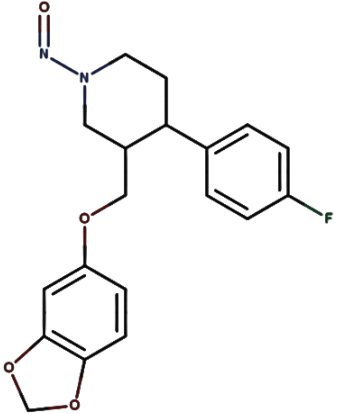
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-methylphenidate	Methylphenidate	-	1300
	N-nitroso-metoprolol	Metoprolol	4	1500
	N-nitroso-mirabegron	Mirabegron	3	400
	N-nitroso-morpholine	Multiple sources	-	127

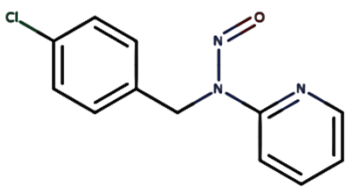
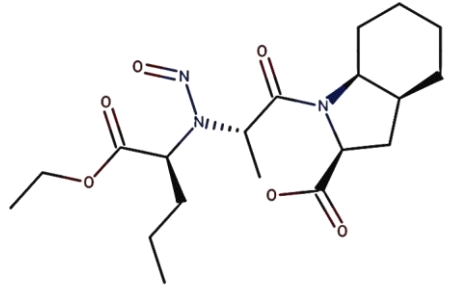
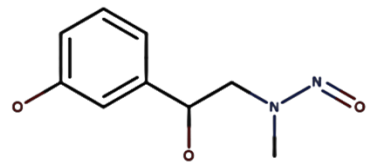
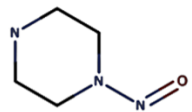
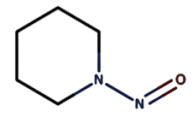
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-moxifloxacin	Moxifloxacin	4	1500
	N-nitroso-nebivolol	Nebivolol	4	1500
	N-nitroso-N-ethyl-valaciclovir	Valaciclovir	3	400
	N-nitroso-N-methyl-4-aminobutyric acid	Multiple sources	-	96

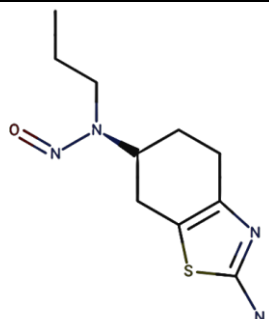
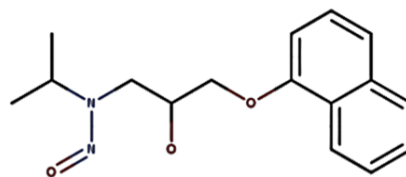
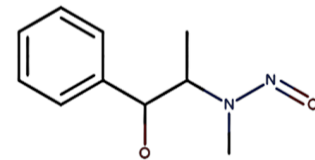
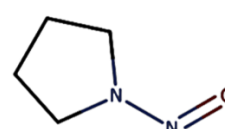
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-N-methyl-valaciclovir	Valaciclovir	3	400
	N-nitroso-nortriptyline	Amitriptyline, Nortriptyline	-	8
	N-nitroso-paroxetine	Paroxetine	-	1300

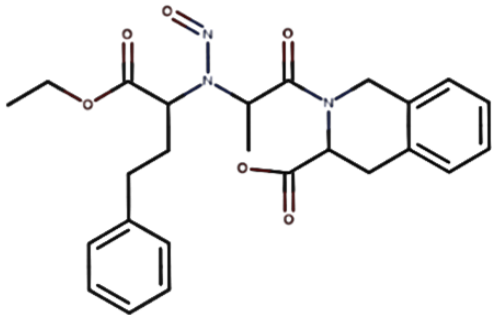
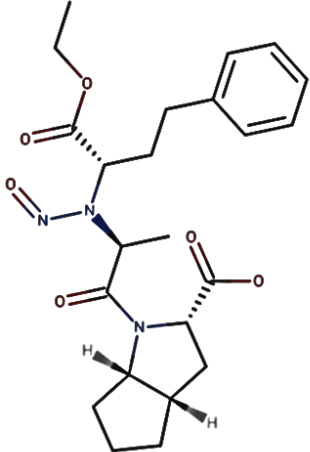
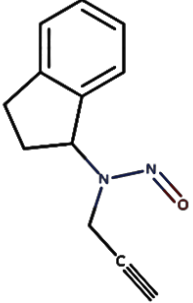
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-p-chloro-benzylamino-pyridine	Chloropyramine	2	100
	N-nitroso-perindopril	Perindopril	5	1500
	N-nitroso-phenylephrine	Phenylephrine	2	100
	N-nitroso-piperazine	Multiple sources	3	400
	N-nitroso-piperidine	Multiple sources	-	1300

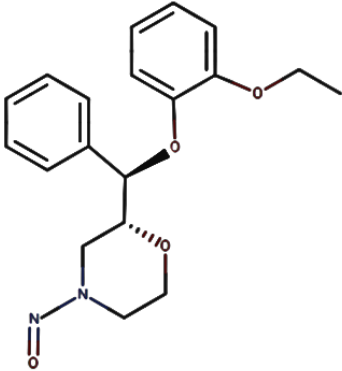
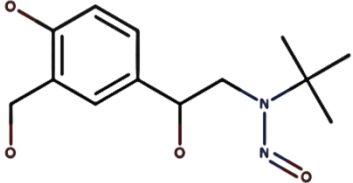
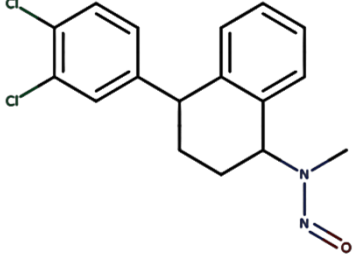
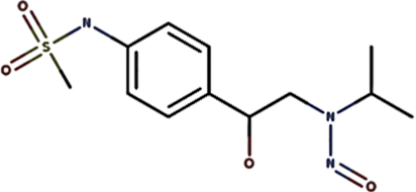
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-pramipexole	Pramipexole	3	400
	N-nitroso-propranolol	Propranolol	4	1500
	N-nitroso-pseudoephedrine	Pseudoephedrine	4	1500
	N-nitroso-pyrrolidine	Multiple sources	-	1700

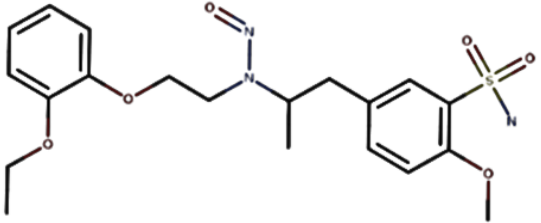
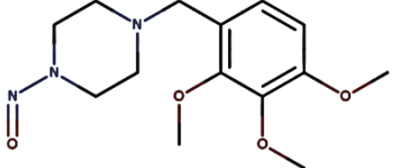
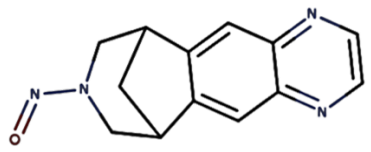
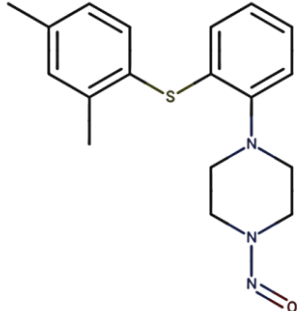
Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
 <p>The structure shows a quinapril core with an N-nitroso group attached to the nitrogen atom of the lactam ring. The quinapril core consists of a benzene ring fused to a six-membered lactam ring, which is further fused to a six-membered ring containing a carbonyl group and a propyl chain. The propyl chain is substituted with a benzyl group and an ethyl ester group.</p>	N-nitroso-quinapril	Quinapril	-	Can be controlled according to ICH Q3A/B
 <p>The structure shows a ramipril core with an N-nitroso group attached to the nitrogen atom of the lactam ring. The ramipril core consists of a bicyclic system (8-azabicyclo[3.2.1]octane) fused to a six-membered lactam ring. The lactam ring is substituted with a propyl chain and a propyl ester group. The propyl chain is further substituted with a benzyl group.</p>	N-nitroso-ramipril	Ramipril	5	1500
 <p>The structure shows a rasagiline core with an N-nitroso group attached to the nitrogen atom. The rasagiline core consists of a benzene ring fused to a five-membered ring, which is further fused to a five-membered ring containing a propyl chain. The propyl chain is substituted with an ethyl group.</p>	N-nitroso-rasagiline	Rasagiline	2	100

Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
 <p>The structure shows a piperazine ring with an N-nitroso group. One of the piperazine nitrogens is substituted with a 1-phenylethyl group, and the other is substituted with a 1-(3-ethoxyphenyl)ethyl group.</p>	N-nitroso-reboxetine	Reboxetine	-	127
 <p>The structure shows a salbutamol molecule where the secondary amine is substituted with an N-nitroso group.</p>	N-nitroso-salbutamol	Salbutamol	5	1500
 <p>The structure shows a sertraline molecule where the secondary amine is substituted with an N-nitroso group.</p>	N-nitroso-sertraline	Sertraline	-	1500
 <p>The structure shows a sotalol molecule where the secondary amine is substituted with an N-nitroso group.</p>	N-nitroso-sotalol	Sotalol	4	1500

Appendix 1: HSA recommended acceptable intake for certain known nitrosamines

Structure	Name	Source (non-exhaustive)	CPCA Category (if applicable)	Recommended AI (ng/day)
	N-nitroso-tamsulosin	Tamsulosin	4	1500
	N-nitroso-trimetazidine	Trimetazidine	3	400
	N-nitroso-varenicline	Varenicline	3	400
	N-nitroso-vortioxetine	Vortioxetine	3	400