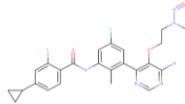
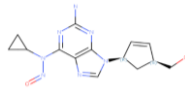
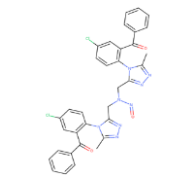
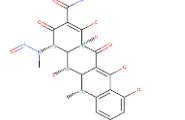
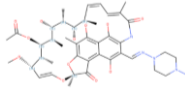
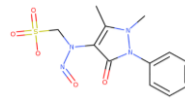
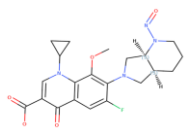
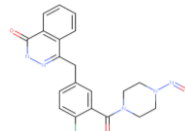
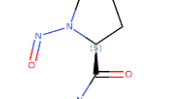
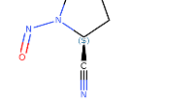
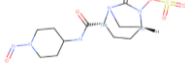
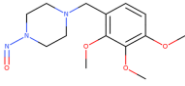


1 June 2026
EMA/42261/2025/Rev. 13
Non-clinical Working Party (NcWP)

Acceptable intakes (AIs) established for N-nitrosamines
Appendix 1 to Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products

The below acceptable intake levels (AIs) have been established by the Non-clinical Working Party (NcWP) and, where applicable, determined using the Carcinogenic Potency Categorization Approach (CPCA).
These limits are applicable only if a FP contains a single N-nitrosamine.
The source refers to potential presence of nitrosamine impurities with structures derived from active substances or their related impurities. This does not mean that the impurity will be found in all products or pharmaceutical forms containing the named API. Please refer to [Q&A](#) on the risk factors for the presence of nitrosamines for further details.

Structure	Name	IUPAC name	SMILES	CAS RN	Synonym/ Acronym	Source	CPCA Category	AI (ng/day)	Note	Publication date	previous AI
	N-nitroso-N-des(prop-2-enoyl)-remibrutinib	N-(3-(6-Amino-5-(2-(methyl(nitroso)amino)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide	CN(CCOC1=C(C2=C(C)C(NC(C3=CC=C(C4CC4)C=C3F)=O)=CC(F)=C2)N=CN=C1N)N=O	NA	LOU064-F8-NO	Remibrutinib		100	Limit derived using structure-activity-relationship, physicochemical features and weight of evidence approach using the TD50 of NNK as point of departure	01 June 2026 (new)	
	N-nitroso-abacavir	N-[2-amino-9-[(1R,4S)-4-(hydroxymethyl)cyclopent-2-en-1-yl]purin-6-yl]-N-cyclopropylnitrous amide	C1CC1N(C2=NC(=NC3=C2N=CN3[C@@H](4)C[C@H](C=C4)CO)N)N=O	NA		Abacavir	5	1500		01 June 2026 (new)	
	N-nitroso-alprazolam EP Impurity H	N,N-bis[(4-(2-benzoyl-4-chlorophenyl)-5-methyl-4H-1,2,4-triazol-3-yl)methyl]nitrous amide	CC=1N(C(=NN=1)CN(CC=4N(C3=C(C(=O)C=2C=CC=CC=2)C=C(C)C=C3)C(=NN=4)C)N=O)C6=C(C(=O)C=5C=CC=CC=5)C=C(C)C=C6	NA		Alprazolam		1500	Limit based on negative bacterial reverse mutation test	01 June 2026 (new)	
	N-nitroso-desmethyl-doxycycline	(4S,5S,6R,12aR)-1,5,10,11,12a-pentahydroxy-6-methyl-4-[methyl(nitroso)amino]-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide	C[C@@H]1C2[C@@H](C3[C@@H](C(=O)C(=C[C@H]3(C(=O)C2=C(C4=C1C=CC=C4O)O)O)C(=O)N)N(C)N=O	NA		Doxycycline	3	400		01 June 2026 (new)	
	N-nitroso-desmethyl-rifampicin	N-nitroso-desmethyl-rifampicin	C=25C(/C=N/N1CCN(CC1)N=O)=C(C=3C(C=2O)=C(C(=C4C=3C((C@)(O4)(C)O)/C=C/[C@H](OC)[C@H]([C@@H](C)[C@@H]([C@H](O)[C@H]([C@H](O)[C@@H](O)[C@@H](O)/C=C/C=C(C(=N5)=O)C)C)C)=O)C)O).OC(=O)C	NA		Rifampicin	3	400		01 June 2026 (new)	
	N-nitroso-metamizole impurity E	[(1,5-dimethyl-3-oxo-2-phenylpyrazol-4-yl)-nitrosoamino]methanesulfonic acid	CC1=C(C(=O)N(N1C)C2=CC=CC=C2)N(CS(=O)(=O)O)N=O	NA		Metamizole	4	1500		01 June 2026 (new)	

Structure	Name	IUPAC name	SMILES	CAS RN	Synonym/ Acronym	Source	CPCA Category	AI (ng/day)	Note	Publication date	previous AI
	N-nitroso-moxifloxacin	1-cyclopropyl-6-fluoro-8-methoxy-7-((4aS,7aS)-1-nitrosooctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	<chem>O=C(C1=CN(C2CC2)C3=C(C=C(F)C(N(C4)C[C@@]5([H]))[C@@]4([H]))CCCN5N=O)=C3OC)C1=O)O</chem>	NA		Moxifloxacin	4	1500	CPCA derived AI as substance showed inconclusive results in in vivo mutagenicity study	01 July 2023 (update)	1500 ng/d - CPCA CAT 4
	N-nitroso-N-des cyclopropanecarbaldehyde olaparib	4-(4-Fluoro-3-(4-nitrosopiperazine-1-carbonyl)benzyl)phthalazin-1(2H)-one	<chem>O=C3NN=C(CC2=CC=C(F)C(C(N1CCN(N=O)CC1)=O)=C2)C4=C3C=CC=C4</chem>	2742659-74-9		Olaparib			Active substance itself is clastogenic. Can be controlled according to ICH Q3A/B.	01 March 2026 (update)	AI 400 ng/day CPCA CAT 3
	N-nitroso-prolinamide	(S)-1-Nitrosopyrrolidine-2-carboxamide	<chem>C1C[C@H]([N(C1)N=O])C(=O)N</chem>	NA		Vildagliptin	4	1500		01 June 2026 (new)	
	N-nitroso-prolinenitrile	(S)-1-Nitrosopyrrolidine-2-carbonitrile	<chem>C1C[C@H]([N(C1)N=O])C#N</chem>	NA		Vildagliptin	4	1500		01 June 2026 (new)	
	N-nitroso-relebactam	(1S,2R,5R)-2-((1-nitrosopiperidin-4-yl)carbamoyl)-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl hydrogen sulfate	<chem>O=S(O)(ON3[C@]2([H])CC[C@H](C(NC1CCN(N=O)CC1)=O)N(C2)C3=O)=O</chem>	NA		Relebactam	3	400		01 June 2026 (new)	
	N-nitroso-trimetazidine	1-nitroso-4-[(2,3,4-trimethoxyphenyl)methyl]piperazine	<chem>COC1=C(C(=C(C=C1)CN2CCN(CC2)N=O)OC)O</chem>	92432-50-3	NTMZ	Trimetazidine		13000	Limit based on the BMDL10 for the most sensitive tissue and gender from a robust rat carcinogenicity study conducted with NTMZ. Nitrosamine with sufficiently robust toxicological data to serve as point of departure for derivation of other AIs by SAR and read-across.	01/07/2023 (update)	AI 400 ng/day CPCA CAT 3