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INFORMATION NOTE:

N-nitrosamines and Tuberculosis Medicines Rifapentine and Rifampicin

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Originally published February 2021
Revised March 2023

Unitaid
Innovation in Global Health

TAG
Treatment Action Group

CLINTON HEALTH ACCESS INITIATIVE

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Background: N-nitrosamines and our medicines

In 2018, health authorities in the European Union, the United States, Canada, and other countries began investigating the presence of N-nitrosamine impurities in medicines. Initially, an N-nitrosamine called N-nitrosodimethylamine (NDMA) was identified in certain antihypertensive drugs. Since then, health authorities have identified N-nitrosamines in several other categories of drugs, including in common heartburn products (ranitidine, nizatidine), in antidiabetic drugs (metformin), and, more recently, in medicines used to treat and prevent tuberculosis (rifapentine, rifampicin).

This information note focuses on the presence of N-nitrosamines in tuberculosis (TB) medicines. The information provided is intended to help health care providers, policymakers, advocates, and other stakeholders understand how the identification of N-nitrosamines in rifapentine and rifampicin may affect the safety and supply of TB medicines, and what this may mean for TB programs and persons affected by TB. Key takeaway messages are presented first, immediately following this introduction, to focus readers' attention on priority actions; subsequent sections present the evidence behind these messages. An accompanying Q&A document answers questions that people taking a course of TB preventive treatment (TPT) or a TB treatment regimen with either rifapentine or rifampicin would want to know about N-nitrosamines before beginning treatment.

Everyone has an intuitive sense of toxicology, or instinctual ideas about what is safe versus dangerous.[1] Words such as "impurity," "carcinogen," and "toxicity" evoke strong emotions and may mean different things to different people. A useful framework to assess the risk of taking a treatment versus the benefit gained is the "risk-benefit ratio." Health care providers, regulators, and guideline bodies will review treatments regularly and review new data in light of the risk-benefit for persons affected by TB. This can change as the new data are made available and factored into the risk-benefit assessment. The perspective of the team discerning the risk-benefit can also change the perception of risk — i.e., health care providers will consider this on a personal level with an individual, while guideline bodies and regulators need to assess the risk from a population perspective. When making decisions about treatment plans, it is important that persons affected by TB have conversations about risk-benefit ratios together with health care professionals to help them to personalize these considerations. When considering any chemical risk — especially one only recently recognized, as in the case of N-nitrosamines in TB medicines — we need to train our 'intuitive toxicology' to judge risks not in isolation, but in the full context of what is known about the choices before us.

In this spirit, this document shares information about N-nitrosamines and health in the context of TB, a life-threatening infectious disease. Not every question about TB medicines and N-nitrosamines has a simple answer, but as a community of people working to end TB, we can decide how to respond together if we are all well informed.

Key Messages and Recommendations

1. Rifapentine and rifampicin are essential medicines for the treatment and prevention of TB. TB is a life-threatening infectious disease, and its prevention and treatment are personal and public health imperatives.

2. Everyone is exposed to some level of N-nitrosamines in daily life. N-nitrosamines are not unique to rifapentine and rifampicin, and their identification in medicines is not a new problem. Rather, in recent years, health authorities and manufacturers have newly recognized the issue and regulators have required manufacturers to take action to document, understand, and reduce the level of N-nitrosamines in medicines.

3. The known risks of not treating or preventing TB outweigh the theoretical risk of cancer associated with N-nitrosamine exposures from rifapentine and rifampicin.

For persons affected by TB:

- People with TB should continue to take TB treatment with rifampicin. If they have concerns, then they should discuss these with their health care provider.
- People at risk of TB should have the option to take preventive treatment based on either rifapentine or rifampicin. These regimens are shorter and more tolerable than alternative regimens, such as isoniazid preventive treatment, and may therefore be preferred by persons affected by TB even in light of the presence of N-nitrosamines. If they have concerns, then they should discuss these with their health care provider.

For health care providers:

- Health care providers should continue to prescribe rifapentine and rifampicin for the prevention and treatment of TB in accordance with clinical guidelines and product information. Continued use of rifapentine and rifampicin is in line with the determination by health authorities that the risk to persons affected by TB from not taking these medicines far outweighs any potential risk from N-nitrosamines. Based on current guidelines, there is no recommended alternative to rifapentine- or rifampicin-containing regimens for treating drug-susceptible TB.
- As a general principle, people have a right to information on the medicines they are taking. Health care providers should answer questions about N-nitrosamines and develop ways to discuss risk-benefit with persons affected by TB. TB programs may consider incorporating information on N-nitrosamines and TB medicines into pre-treatment counseling. This information should be presented in a way that promotes a full understanding of the associated risks, emphasizes the importance of preventing and treating TB, and outlines the pros/cons of alternative treatment regimens (if available).

For manufacturers:

- Manufacturers of rifapentine should expeditiously implement remediation plans with the goal of reducing the presence of CPNP N-nitrosamine impurity toward the target acceptable intake of 0.1 ppm and communicate transparently on their progress. In the interim, manufacturers must test all batches before drug release to ensure the interim limit of 20 ppm is met. Only final pharmaceutical product containing CPNP at or below 20 ppm will be released and distributed to persons affected by TB.
- Manufacturers of rifampicin should expeditiously implement remediation plans with the goal of reducing the presence of MNP N-nitrosamine impurity to the target acceptable intake of 0.16 ppm and communicate transparently on their progress. In the interim, manufacturers must test all batches before drug release to ensure the interim limit of 5 ppm is met. Only final pharmaceutical product containing MNP at or below 5 ppm will be released and distributed to persons affected by TB.

For governments:

- Ministries of health and national TB programs should verify that any deliveries of rifapentine or rifampicin come with a certificate of analysis testifying that the associated product batch tested at or below the interim limits adopted by the WHO prequalification program.
- Regulators and quality-assurance mechanisms should continue to guide industry on N-nitrosamine remediation. When revising interim limits, regulators should grant manufacturers sufficient time to meet new standards in order to avoid drug shortages and stockouts.

For advocates and civil society:

- TB advocates and civil society should closely monitor global and local supply chains to avert shortages and stockouts of rifapentine and rifampicin.
- TB advocates and civil society should support the treatment literacy of TB-affected communities to build public confidence in the safety of TB medicines.
- TB advocates and civil society should hold rifapentine and rifampicin manufacturers accountable for implementing N-nitrosamine remediation plans according to clear, time-bound milestones.
- TB advocates and civil society should ask national drug regulatory authorities and ministries of health how they are responding to the risk of N-nitrosamines in rifapentine and rifampicin, including for locally manufactured products that fall outside the scope of stringent regulatory bodies or WHO prequalification.

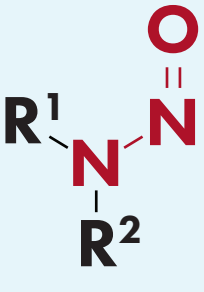
What are N-nitrosamines?

N-nitrosamine is a general term used to designate a vast group of N-nitroso compounds, or chemical compounds with a common functional group ($R^1R^2N–N=O$). The terms "nitrosamine" and "N-nitrosamine" are used interchangeably.

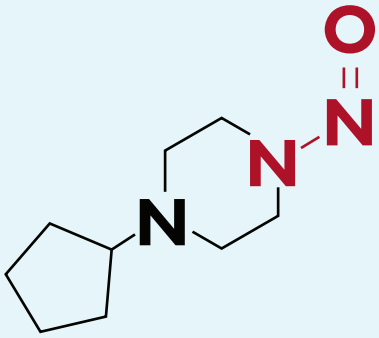
Based primarily on data from animal models, N-nitrosamines are considered potent genotoxic agents. This means that N-nitrosamines can damage the genetic information within cells, leading to mutations that may cause cancer. Most N-nitrosamines are mutagenic (i.e., having the ability to cause a permanent change in an organism's genes). For this reason, the International Agency for Research on Cancer classifies N-nitrosamines as probable or possible human carcinogens.[2] Not all N-nitrosamines are equally carcinogenic. There are extensive differences in potency between different N-nitrosamines, with the most potent being the so-called volatile N-nitrosamines, such as NDMA. Most evidence supporting a causal relationship between N-nitrosamines and cancer comes from studies in animals, and observational studies in humans have raised an association between exposure to certain nitrosamines and cancer.[3]

The nitrosamine impurity found in rifapentine is called 1-cyclopentyl-4-nitrosopiperazine (**CPNP**) (CAS 61379-66-6).

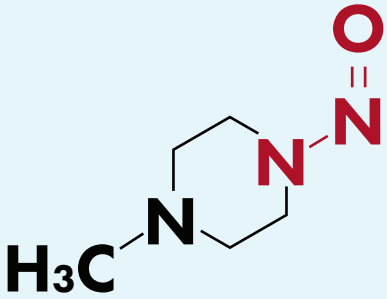
The nitrosamine impurity found in rifampicin is called 1-methyl-4-nitrosopiperazine (**MNP** or **MeNP**) (CAS 16339-07-4).



General N-nitrosamine Structure



1-cyclopentyl-4-nitrosopiperazine (**CPNP**)



1-methyl-4-nitrosopiperazine (**MNP** or **MeNP**)

Where do N-nitrosamines come from?

Everyone is exposed to some level of N-nitrosamines in daily life. N-nitrosamines are found in drinking water, in foods (including processed foods, cured or grilled meats, dairy products, and vegetables), from direct and indirect tobacco exposure, and from contact with some latex and rubber products.[4] Table 1 (Appendix, p. 13) shows the estimated daily and annual exposure to NDMA from processed meats in adults in the European Union and the total mean (average) background exposure of NDMA from contaminated beverages and food and air and water pollution. In many cases, N-nitrosamine exposures from medicines are similar to dietary exposures. Based on tests for N-nitrosamine impurities in ranitidine (a heartburn medication), in 2019 the U.S. Food and Drug Administration (FDA) concluded that these drugs contain no more NDMA than what would be expected from common foods like grilled or smoked meats.[5,6]

Not all medicines contain N-nitrosamines, but for those that do, the resulting impurities can arise from several factors. N-nitrosamines may be present in the active pharmaceutical ingredients (APIs) used to make finished pharmaceutical products (FPPs). Their presence may be linked to drug synthesis processes, accidental introduction due to cross-contamination (e.g., when using already contaminated equipment or reagents), recovery procedures for solvents, or degradation of APIs, due to their inherent structure, during storage.[7] The formation of an N-nitrosamine impurity can be specific to a product or nonspecific.

The World Health Organization (WHO) maintains that although nitrosamines are present in daily life, "their presence in medicines is nonetheless considered unacceptable."[8] For this reason, the WHO and national drug regulators are proactively working with manufacturers to identify and reduce the presence of N-nitrosamines in medical products. The FDA and the European Medicines Agency (EMA) have shared guidance for industry on the control of N-nitrosamines, and the FDA has published testing methods that industry can use to detect N-nitrosamine impurities.[9,10] The Committee for Medicinal Products for Human Use at the EMA asked marketing authorization holders to review all chemical and biological human medicines for the presence of N-nitrosamines and test products at risk. The deadline for returning the risk evaluations to the EMA was March 31, 2021. Similarly, in April 2020 the WHO Prequalification Unit–Medicines Team (PQT/MED) advised companies to conduct risk assessments to evaluate the potential presence of N-nitrosamine impurities for all API and medicines applications.[11] For rifapentine and rifampicin, specifically, the WHO PQT/MED requested that all rifapentine and rifampicin API and medicines applicants test for CPNP and MNP impurities in a representative number of batches.[12]

N-nitrosamines and rifapentine

WHO PQT/MED has prequalified two rifapentine-based finished pharmaceutical products to date: Sanofi's 150 mg rifapentine standalone tablet (Priftin®) and Macleods Pharmaceuticals' isoniazid/rifapentine 300 mg/300 mg film-coated tablet. For Priftin®, which is prequalified based on FDA approval, Sanofi has continued providing regular updates to PQT/MED. Given the critical role this medicine plays in public health, the FDA continues to permit the temporary distribution of Priftin® tablets with CPNP impurity content at or below 20 parts per million (ppm) while the manufacturer works on corrective measures.

In May 2022, PQT/MED prequalified the first isoniazid/rifapentine (INH/RPT) generic product (isoniazid/rifapentine 300 mg/300 mg film-coated tablet, Macleods Pharmaceuticals Ltd.) with an interim release limit of not more than 20 ppm for CPNP impurity, established based on risk-benefit considerations and process capability. The interim limit will be reviewed regularly. Similarly, rifapentine API from Macleods Pharmaceuticals Ltd. has been accepted with an interim release limit for CPNP based on process capability.[13] In addition, Lupin has Global Fund Expert Review Panel (ERP) approval for INH/RPT 300/300 mg and RPT 300 mg products with the same interim CPNP release limit.

According to a risk assessment conducted and shared by Sanofi, the N-nitrosamine impurity identified in rifapentine, CPNP, originates from the synthesis of rifapentine API. More specifically, CPNP arises from an intermediate step in the production of one of the starting materials of the final API and consequently is present in the final API as an impurity.[14]

Sanofi observed an increased level of CPNP impurity in samples of rifapentine FPP compared with the level of impurity found in the corresponding API batch. This may be due to the oxidation of residual starting material or the hydrolysis of rifapentine into a substance of degradation during some of the drug product processing steps (e.g., granulation, coating, etc.) or on standing.[15]

In other words, CPNP is intrinsic to the rifapentine active ingredient itself. Consequently, this problem is not particular to Sanofi; all rifapentine manufacturers will need to address N-nitrosamine impurities. It is possible to reduce the amount of N-nitrosamines in rifapentine, but it may not be possible to eliminate N-nitrosamines from rifapentine FPP entirely.

N-nitrosamines and rifampicin

Dozens of companies manufacture rifampicin in a range of formulations and combinations.[16] Unlike for rifapentine, no information has been shared yet on the root cause of MNP in rifampicin (though, as with rifapentine, the impurity likely arises in a similar fashion, from API synthesis). The WHO PQT/MED requested that all prequalified manufacturers of rifampicin API and medicines undertake a risk evaluation for nitrosamine impurities by the end of 2020. The WHO has issued the following information regarding nitrosamine concerns in rifampicin-containing products[17]:

> *"The results provided for all prequalified APIs and Finished Pharmaceutical Products (FPP) show that MNP is present at trace levels in all batches tested. MNP levels have been shown to be below or close to 5 ppm in all API and FPP products tested. PQT/MED has assessed the related nitrosamines risk quality information for all prequalified rifampicin products (APIs and FPPs) taking into consideration toxicological and risk/benefit balance assessments.*
>
> *For all prequalified APIs, interim limits for MNP impurity have been accepted [by WHO] on a temporary basis. These interim limits have been defined based on process capability on a case-by-case [basis] and will be reviewed regularly. Similarly, interim limits are being assessed for the prequalified FPPs.*
>
> *PQT/MED is closely working with the manufacturers to follow up on mitigation measures that should be applied in order to decrease the impurity to lifetime acceptable levels. Mitigation measures may require investigations and time until they can be verified as effective."*

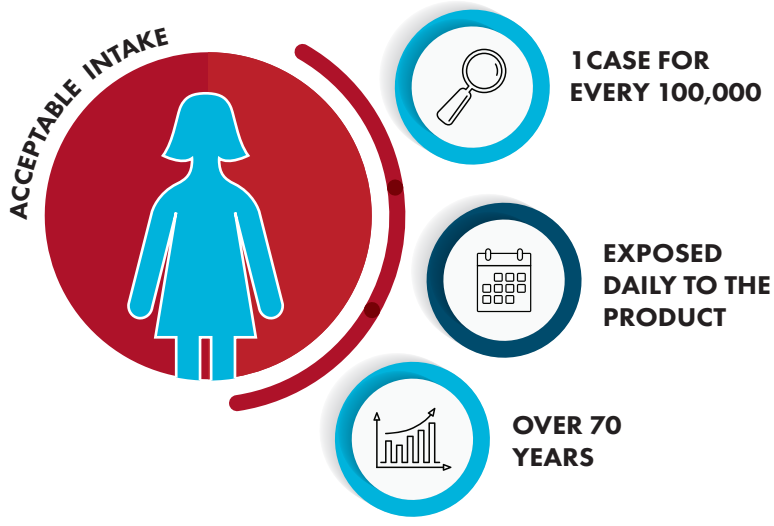
N-nitrosamines, carcinogenicity, and acceptable intake

Ideally, N-nitrosamines should not be present in medicines. But where the presence of N-nitrosamines cannot be eliminated entirely, they should "at least be controlled below a level where human cancer risk associated with the exposure is negligible," according to the WHO.[18] The sections below describe how such levels are determined.

Acceptable intake

There are no available data to directly evaluate the carcinogenic potential of CPNP and MNP in humans. In the absence of direct data, the "acceptable level" of N-nitrosamines is defined by a measure called acceptable intake (AI). The method for determining AI is set by the internationally recognized ICH M7(R1) guideline.[19] Most succinctly, AI is defined as the intake level associated with a theoretical excess lifetime cancer risk of 1:100,000. In other words, the AI limit is a daily exposure to a compound that approximates a 1:100,000 cancer risk after 70 years of daily exposure (i.e., 1 case for every 100,000 exposed daily to the product over 70 years). Most simply, AI is the intake level that poses a negligible cancer risk.

The ICH M7(R1) recommends calculating a compound-specific AI based on rodent carcinogenicity potency data such as TD_{50} values (doses giving a 50% tumor incidence in rodents). The TD_{50} is used as the point of departure for calculating the dose associated with a theoretical excess cancer risk of 1:100,000 in humans.[20] Once calculated, the AI is converted into a measure of ppm. The conversion of AI into ppm varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label: AI (ppm) = AI (ng) / MDD (mg). Converting AI into ppm gives a measure of acceptable N-nitrosamine concentration in an API, which can be monitored by manufacturers and regulators.



If N-nitrosamines without published AI limits are found in drug products, manufacturers should use the approach outlined in ICH M7(R1) to determine the risk associated with the N-nitrosamine and contact the regulatory agency about the acceptability of any proposed limit. This is what happened in the case of CPNP and MNP. To set the AI for CPNP in rifapentine and MNP in rifampicin, the FDA proposed to apply the long-term AI of a different nitrosamine called NDMA (**96 ng/day**). This corresponds to:

- not more than (NMT) **0.1 ppm for CPNP in rifapentine**.
- NMT **0.16 ppm for MNP in rifampicin**.

CPNP and MNP may be less carcinogenic than NDMA (based on an analysis of molecular structure), so by applying the long-term AI of NDMA, the FDA has taken a conservative approach to setting the AIs for CPNP and MNP.[21] The FDA has further advised that the same AIs apply regardless of whether medicines are taken by adults or children. When asked about the matter, the agency specified: "Although longer exposures will increase cancer risk and therefore the concern for pediatric persons affected by TB, the acceptable intake calculations [for rifapentine and rifampicin] are sufficiently conservative that no adjustments are needed to account for exposures in children."[22]

Based on a benefit/risk assessment, Sanofi proposed to the FDA that they would monitor the level of CPNP in rifapentine API and FPP batches with an interim limit of ≤20 ppm at FPP release (i.e., when the product is released for sale onto the market). In a communication dated October 29, 2020, the FDA accepted Sanofi's proposal. While the AI limit is 0.1 ppm for CPNP in rifapentine, the agency will not object to certain manufacturers temporarily distributing rifapentine containing CPNP at or below 20 ppm until they can reduce or eliminate the impurity.[23] This interim limit is higher than the AI and would allow for the continued marketing and use of rifapentine during a transition period while a remediation plan is implemented to reduce the content of CPNP toward the AI limit.

The WHO PQT/MED endorsed the FDA's proposed higher limits for rifapentine. The same 20 ppm interim limit applies to rifapentine manufactured by Macleods and the rifapentine products manufactured by Lupin.[24] Therefore, Sanofi, Macleods, and Lupin may release drug and distribute in compliance with this higher 20 ppm interim limit. The level of impurity must be reported for each batch of FPP at release and be presented on a certificate of analysis available to buyers.

This followed a similar communication concerning rifampicin by the FDA dated August 8, 2020. While the AI limit is 0.16 ppm for MNP in rifampicin, the agency will not object to certain manufacturers temporarily distributing rifampicin containing MNP at or below 5 ppm until they can reduce or eliminate the impurity.[25]

Less-than-lifetime exposure

The AI approximates a 1:100,000 risk of cancer over a lifetime (70 years) of daily dosing. Not every medicine is taken every day for life. For these medicines, a concept called less than lifetime (LTL) can allow for higher daily intake of N-nitrosamines than would be the case for lifetime exposure while maintaining comparable risk between regimens taken daily for life and those taken for a shorter duration or less frequently. The process for determining LTL is set forth in ICH M7(R1).

At the current time, neither the FDA nor WHO PQT/MED accept applying the LTL exposure limits for CPNP or MNP, so the 70-year exposure AI limits apply.

Making sense of different risks

How does CPNP exposure from rifapentine and MNP exposure from rifampicin compare to background exposure to other N-nitrosamines?

Rifapentine is used in the following two recommended TB preventive treatment regimens:

The 3HP regimen: rifapentine and isoniazid taken once a week for 12 weeks (three months).

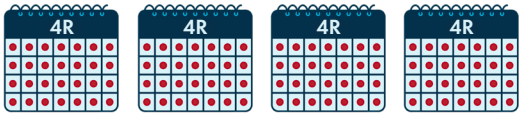
The 1HP regimen: rifapentine and isoniazid taken daily for four weeks (one month)

Rifapentine is also used in the new four-month TB treatment regimen HPZM (**2HPZM/2HPM**). Sometimes called the Study 31 regimen, this regimen involves taking rifapentine together with three other drugs (isoniazid, pyrazinamide, and moxifloxacin) for two months followed by two months of rifapentine, isoniazid, and moxifloxacin. Treatment is taken daily.

As shown in **Table 2** (Appendix, p. 13), the exposure to carcinogenic risk when taking the rifapentine-based 3HP or 1HP regimens for TB preventive treatment approximates one year of total background exposure to NDMA (from beverages and food, or air and water pollution) in high-income countries (HICs). Exposure to nitrosamines when taking rifapentine in the Study 31 four-month TB treatment regimen (2HPZM/2HPM) is equivalent to eight years of total background exposure. This assumes that cancer risk with CPNP is equivalent to that with NDMA.

Table 3 (Appendix, p. 14) shows the corresponding comparison of background exposure to exposure to carcinogenic risk when taking rifampicin-based regimens. Rifampicin is taken as part of the standard six-month TB treatment regimen known as HRZE (**2HRZE/4HR**), which involves taking rifampicin together with three other drugs (isoniazid, pyrazinamide, and ethambutol) for two months followed by four months of rifampicin and isoniazid. Treatment is taken daily. Rifampicin is also used in the following two recommended TB preventive treatment regimens:

The 3HR regimen: rifampicin and isoniazid taken daily for three months.



The 4R regimen: rifampicin taken daily for four months.

Impact on TB drug supply

Health authorities have acknowledged that the risk to persons affected by TB from not taking their rifapentine or rifampicin medicines far outweighs any potential risk from CPNP or MNP.[26,27] Therefore, health care professionals should continue to prescribe rifapentine and rifampicin as normal in accordance with clinical guidelines and product information.

All batches of rifapentine released by Sanofi, Macleods, and Lupin are being tested to ensure the drug product meets the CPNP temporary limit of 20 ppm as accepted by the FDA and recognized by the WHO PQT/MED. The initial identification of CPNP impurities caused manufacturers to either pause or slow production throughout 2020 while they investigated the issue, worked with regulators to establish intake limits, and devised remediation plans. This resulted in delays in shipping rifapentine to countries, and many clinical trials studying rifapentine-based TB preventive treatment regimens had to either pause enrollment or slow activities. Sanofi resumed production of rifapentine in December 2020, and in the same month Macleods received endorsement for its 3HP fixed-dose combination tablet from the ERP.[28] Since then, Macleods' product has been prequalified by the WHO, and the Lupin rifapentine products are now endorsed for use by ERP. As of 2023, there are no supply concerns with any rifapentine formulations.

Based on current guidelines, there is no recommended alternative to rifapentine- or rifampicin-containing regimens for treating drug-susceptible TB. According to the WHO, people taking TB treatment should continue treatment with rifampicin as usual unless advised otherwise by a health care professional.[29] To date, there has been no observed impact on access to rifampicin.

The requirement for suppliers to do additional testing for CPNP and MNP impurities and to implement remediation plans to reduce the level of these N-nitrosamines may result in price increases for rifapentine and rifampicin products. For now, the rifapentine prices negotiated by Unitaid and its partners with Sanofi, Macleods, and Lupin remain in effect for eligible countries.[30,31,32] TB programs should remain vigilant for the possibility of higher prices, and TB advocates and civil society should closely monitor global and local supply chains to avert shortages and stockouts of rifapentine and rifampicin.

The bottom line

Rifapentine and rifampicin remain essential medicines for the prevention and treatment of TB.

The identification of N-nitrosamine impurities in rifapentine and rifampicin should not stop people from receiving TB treatment or preventive treatment. Health authorities have established temporary interim limits allowing manufacturers to distribute rifapentine FPP containing CPNP at ≤20 ppm and rifampicin FPP containing MNP at ≤5 ppm. Manufacturers are working with the goal of reducing N-nitrosamine impurities to the respective AI limits of 0.1 ppm (for CPNP) and 0.16 ppm (for MNP). All stakeholders invested in ending TB should work together to ensure the safety of, and public confidence in, TB medicines.

APPENDIX

Table 1. Estimated Food and Total Background Exposure to NDMA

Source of NDMA exposure	Estimated exposure in µg/day	Estimated annual exposure in µg
Processed meats in adults in European Union* (lifetime daily)	0.025 µg/day to 0.085 µg/day	9 µg/year to 31 µg/year
Total mean background exposure† (lifetime daily)	0.1 µg/day to 1 µg/day	36.5 µg/year to 365 µg/year

**Source: EFSA Panel on Food Additives and Nutrient Sources added to Food. Re-evaluation of potassium nitrite (E 249) and sodium nitrite (E 250) as food additives. EFSA J. 2017;15(6):e04786. doi: 10.2903/j.efsa.2017.4786.*

†Total background exposure from contaminated beverages and food and air and water pollution. Estimates in the literature vary widely. The values given here are order-of-magnitude estimates for the lower and upper range of NDMA exposure based on the two following publications:

Keszei A, Goldbohm RA, Schouten LJ, et al. Dietary N-nitroso compounds, endogenous nitrosation, and the risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. Am J Clin Nutr. 2013;97(1):135–46. doi: 10.3945/ajcn.112.043885.

Gushgari, A.J, Halden RU. Critical review of major sources of human exposure to N-nitrosamines. Chemosphere. 2018;210:1124–36. doi: 10.1016/j.chemosphere.2018.07.098.

Table 2. CPNP Exposure from Rifapentine-Containing Regimens Compared with NDMA Background Exposure in HIC

Regimen (indication)	Dose and duration of treatment	Interim acceptable CPNP content	Total CPNP exposure per regimen	Approximation to NDMA background exposure (365 µg per year – see Table 1)
1HP (TB infection)	600 mg daily for 4 weeks = 28 doses	20 ppm	28 × 600 mg × 20 ppm = **336 µg**	336 µg/365 µg = **~0.9 years**
3HP (TB infection)	900 mg weekly for 12 weeks = 12 doses	20 ppm	12 × 900 mg × 20 ppm = **216 µg**	216 µg/365 µg = **~0.6 years**
Rifaquin (TB disease)	600 mg twice weekly for 8 weeks, then 600 mg weekly for 16 weeks = 32 doses	20 ppm	32 × 600 mg × 20 ppm = **384 µg**	384 µg/365 µg = **~1.1 years**
2HPZM/2HPM (TB disease)	1200 mg daily for 17 weeks = 119 doses	20 ppm	119 × 1200 mg × 20 ppm = **2856 µg**	2856 µg/365 µg = **~7.8 years**
	1500 mg daily for 17 weeks = 119 doses*		119 × 1500 mg × 20 ppm = **3570 µg**	3570 µg/365 µg = **~9.8 years**
6P† (TB infection)	600 mg daily for 6 weeks = 42 doses	20 ppm	42 × 600 mg × 20 ppm = **504 µg**	504 µg/365 µg = **~1.4 years**

**AIDS Clinical Trials Group A5414 SPECTRA-TB. Dooley K. Current portfolio, enrollments, studies under development, and Current Tuberculosis Transformative Science Group Study Monitoring Committee membership. Presentation at: AIDS Clinical Trials Group Annual Network Meeting; 2022 June 15; Washington, D.C.*

†Regimen under evaluation in clinical trial (https://clinicaltrials.gov/ct2/show/record/NCT03474029); not yet licensed or approved for use.

Drug abbreviations: H = isoniazid; P = rifapentine; Z = pyrazinamide; M = moxifloxacin.

Table 3. MNP Exposure from Rifampicin-Containing Regimens Compared with NDMA Background Exposure in HIC

Regimen (indication)	Dose and duration of treatment	Interim acceptable MNP content	Total MNP exposure per regimen	Approximation to NDMA background exposure (365 µg per year – see Table 1)
2HRZE/4HR (TB disease)	600 mg daily for 24 weeks = 168 doses	5 ppm	168 × 600 mg × 5 ppm = **504 µg**	504 µg/365 µg = **~1.4 years**
4R (TB infection)	600 mg daily for 16 weeks = 112 doses	5 ppm	112 × 600 mg × 5 ppm = **336 µg**	336 µg/365 µg = **~0.9 years**
3HR (calculated at pediatric doses) (TB infection)	75 to 300 mg daily for 12 weeks = 12 doses	5 ppm	12 × 75 mg × 5 ppm = **4.5 µg**	4.5 µg/365 µg = **~0.1 months**
			12 × 300 mg × 5 ppm = **18 µg**	18 µg/365 µg = **~0.6 months**

Drug abbreviations: H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol.

Endnotes

1 Neil N, Malmfors T, Slovic P. Intuitive toxicology: expert and lay judgements of chemical risks. Toxicol Pathol. 1994;22(2):198–201. doi: 10.1177/019262339402200214.

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