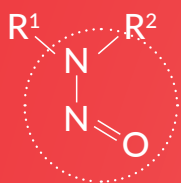


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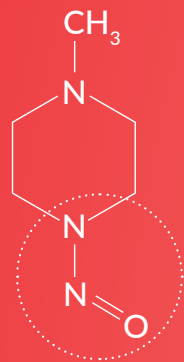
N-nitrosamines and Tuberculosis Medicines Rifampicin and Rifapentine

Written by: Sandrine Cloëz and Mike Frick

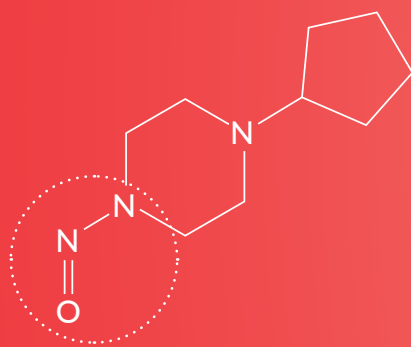
Reviewed by: Jeremy Hill, Lindsay McKenna, Payam Nahid, Regina Osih, Christophe Perrin, Tina Shah, Karin Turner, and staff of the Global Drug Facility



General N-nitrosamine chemical structure



MNP (found in rifampicin)



CPNP (found in rifapentine)

1. 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, a type of 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 (rifampicin, rifapentine).

This information note focuses on the presence of N-nitrosamines in tuberculosis (TB) medicines. The information provided is intended to help advocates, policymakers, and implementers understand how the identification of N-nitrosamines in rifampicin and rifapentine may affect the safety and supply of TB medicines and what this may mean for TB programs and patients. 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. Accompanying Q&A documents answer questions that people taking a course of TB preventive therapy (TPT) or a TB treatment regimen with either rifampicin or rifapentine 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. When considering any chemical risk—especially one only recently recognized, as in the case of N-nitrosamines and 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. Rifampicin and rifapentine 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 rifampicin and rifapentine, and their identification in medicines is not a new problem. Rather, in recent years health authorities and manufacturers have newly recognized the issue and taken 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 rifampicin and rifapentine.



For people with TB:

- People with TB should continue to take TB treatment with rifampicin.
- 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 therapy, and may therefore be preferred by patients even in light of the presence of N-nitrosamines.
- People have a right to information on the medicines they are taking. All people receiving TB treatment and preventive therapy should receive information on N-nitrosamines and TB medicines. 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 to reduce 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 should test all batches before drug release to ensure the interim limit of 20 ppm is met. Any finished pharmaceutical product that tests above 20 ppm should be held back and not distributed to patients.

- Manufacturers of rifampicin should expeditiously implement remediation plans to reduce 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 should test all batches before drug release to ensure the interim limit of 5 ppm is met. Any finished pharmaceutical product that tests above 5 ppm should be held back and not distributed to patients. (Note: this limit may change after the World Health Organization [WHO] and regulatory authorities finalize their reviews of the risk assessment reports provided by rifampicin manufacturers in late 2020.)



For governments:

- Ministries of health and national TB programs should verify that any deliveries of rifampicin or rifapentine come with a certificate of analysis testifying that the associated product batch tested at or below the interim limits set by health authorities. (Note: certificates of analysis for rifampicin-containing products may not be available until after the WHO finishes reviewing the risk assessment reports submitted by rifampicin manufacturers in December 2020. In the interim, programs should continue to use their current rifampicin stock and accept newly delivered product.)
- 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 rifampicin and rifapentine 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 rifampicin and rifapentine, including for locally manufactured products that fall outside the scope of stringent regulatory bodies or WHO prequalification.

2. 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 ($>N-N=O$). 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 rifampicin is called 1-methyl-4-nitrosopiperazine (MNP or MeNP) (CAS 16339-07-4).

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

3. Where do N-nitrosamines come from?

Everyone is exposed to some level of N-nitrosamines in daily life. N-nitrosamines are present 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 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 drug substances during storage.⁷ The formation of an N-nitrosamine impurity can be specific to a product or nonspecific.

The 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 is March 31, 2021. Similarly, in April 2020 the WHO Pre-qualification 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 rifampicin and rifapentine, specifically, the WHO PQT/MED requested that all rifampicin and rifapentine API and medicines applicants test for MNP and CPNP impurities in a representative number of batches.¹²

N-nitrosamines and rifapentine

Currently, only two companies produce quality-assured rifapentine: Sanofi and Macleods.

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.¹³

An increased level of CPNP impurity has been observed in samples of rifapentine FPP compared with the level of impurity found in the corresponding API batch.¹⁴ 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.).

In other words, CPNP is intrinsic to the rifapentine active ingredient itself. Consequently, 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.¹⁵ No information has been shared yet on the root cause of MNP in rifampicin (though, like 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 PQT/MED will complete its review of submitted risk assessment reports in 2021, and more information is expected soon.¹⁶

4. 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.”¹⁷ 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.¹⁸ 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. 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 TD50 values (doses giving a 50% tumor incidence in rodents). The TD50 is used as the point of departure for calculating the dose associated with a theoretical excess cancer risk of 1:100,000 in humans.¹⁹ Once calculated, the AI is converted into a measure of parts per million (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 drug substance, 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 MNP and CPNP. To set the AI for MNP in rifampicin and CPNP in rifapentine, the FDA proposed to apply the long-term interim AI of a different nitrosamine called NDMA (**96 ng/day**). This corresponds to:

- not more than (NMT) **0.16 ppm for MNP** ($96 \text{ ng/day} / 600 \text{ mg/day} = 0.16 \text{ ppm}$).
- NMT **0.1 ppm for CPNP** ($96 \text{ ng/day} / 900 \text{ mg/day} = 0.107 \text{ ppm}$).

MNP and CPNP are likely less carcinogenic than NDMA (based on an analysis of molecular structure), so by applying the long-term interim AI of NDMA, the FDA has taken a conservative approach to setting the AIs for MNP and CPNP.²⁰ 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 patients, the acceptable intake calculations [for rifapentine and rifampicin] are sufficiently conservative that no adjustments are needed to account for exposures in children.”²¹

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).

The LTL approach is an important tool for averting drug shortages while manufacturers work to achieve lower levels of N-nitrosamines. Reducing the level of N-nitrosamines to at or below the AI level takes considerable effort and investment. Depending on the source of the impurity, manufacturers may need to change API sourcing, manufacturing, packaging, or distribution practices. Some medicines affected by N-nitrosamines are considered essential medicines, for which maintaining uninterrupted access to treatment is necessary for maintaining the health of individual patients and/or for safeguarding public health. Other affected medicines may not have clear or equivalent clinical substitutes. In such cases, regulators may establish higher interim limits that temporarily allow for continued use of medicines containing N-nitrosamine concentrations that exceed the AI while manufacturers remediate the problem.

Table 1 illustrates how lifetime exposures are converted into LTL based on frequency of intake and drug dosing, using the threshold of toxicological concern (TTC) of 1.5 µg/day as an example. From this, a multiplier is inferred that is proposed for LTL calculations involving substances that have an AI limit below the TTC.²²

Table 1: Converting from AI to LTL

| Duration of treatment | <1 month | >1- 12 months | >1-10 years | >10 years to lifetime |
|---|----------|---------------|-------------|-----------------------|
| Daily intake (µg/day) | 120 | 20 | 10 | 1.5 |
| Inferred multiplier for other AI limits | 80 | 13.3 | 6.6 | 1 |

Rifapentine: interim acceptable limit for LTL exposure

Most TB prevention and treatment regimens incorporating rifapentine use rifapentine for less than one month:

- 3HP regimen (TB infection): 900 mg of rifapentine taken once weekly for 12 weeks (which equates to 12 days of taking rifapentine, or less than one month of total exposure).
- 1HP regimen (TB infection): 600 mg of rifapentine taken daily for four weeks (which equates to 28 days of taking rifapentine, or less than one month of total exposure).
- Rifaquin regimen (active TB disease): 600 mg of rifapentine twice weekly for two months (which equates to 32 days of taking rifapentine, a duration of approximately one month of total exposure).

Therefore, for the three regimens above, the interim acceptable intake limit using the LTL approach is 7680 ng/day, equaling the proposed AI limit of 96 ng/day multiplied by 80 for medicines taken for less than one month (hereunder referred to as AI-LTL).

Two experimental regimens incorporating rifapentine use rifapentine for more than one month:

- HPZM/Study 31/A5349 regimen (TB disease): 1200 mg of rifapentine daily for four months (which equates to >1 to 12 months of total exposure).
- 6P (TB infection) 600 mg daily for six weeks (which equates to >1 to 12 months of total exposure).

For the two regimens above, the interim acceptable intake limit using the LTL approach would be 1280 ng/day, equaling the proposed AI limit of 96 ng/day multiplied by 13.3 for medicines taken >1 to 12 months (hereunder referred to as AI-LTL).

The conversion of AI-LTL into ppm varies by regimen and is calculated based on the AI-LTL for rifapentine and the quantity of rifapentine taken in each dose, according to the regimen. The formula is: $AI-LTL (ppm) = AI-LTL (ng/day) / dose (mg)$. Table 2 shows the interim AI-LTL for CPNP as calculated for different rifapentine-containing regimens.

Table 2: Interim Acceptable Limit for CPNP in Rifapentine-containing Regimens

| Regimen (indication) | Dose and duration of treatment | Calculation AI-LTL = AI* multiplier | AI-LTL | Calculation Interim acceptable limit in ppm = AI-LTL/MDD | Interim AI-LTL (ppm in API) |
|------------------------------|--|-------------------------------------|-------------|--|-----------------------------|
| 3HP (TB infection) | 900 mg weekly for 12 weeks = 12 days of treatment (<1 month of exposure) | 96 ng/day x 80 | 7680 ng/day | 7680 ng/900 mg | 8.5 ppm |

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| | | | | | |
|--|---|------------------|-------------|-----------------|----------|
| 1HP (TB infection) | 600 mg daily for 4 weeks = 28 days of treatment (<1 month of exposure) | 96 ng/day x 80 | 7680 ng/day | 7680 ng/600 mg | 12.8 ppm |
| Rifampin regimen (TB disease) | 600 mg twice weekly for 2 months then 600 mg weekly for 4 months = 32 days of treatment (<1 month of exposure) | 96 ng/day x 80 | 7680 ng/day | 7680 ng/600 mg | 12.8 ppm |
| 2(HPZM)/2(HPM) Study 31/A5349 regimen^a (TB disease) | 1200 mg daily for 4 months (>1 to 12 months of exposure) | 96 ng/day x 13.3 | 1280 ng/day | 1280 ng/1200 mg | 1.1 ppm |
| 6P^b (TB infection) | 600 mg daily for 6 weeks (>1 to 12 months of exposure) | 96 ng/day x 13.3 | 1280 ng/day | 1280 ng/600 mg | 2.1 ppm |

a. Regimen evaluated in recently completed clinical trial; not yet licensed or approved for use.

β. Regimen under evaluation in clinical trial; not yet licensed or approved for use.

Rifampicin: interim acceptable limit for LTL exposure

The vast majority of rifampicin used for TB is used to treat drug-susceptible TB, though it may also be used for the prevention of TB. The duration of therapy varies depending on the regimen and the indication. Table 3 shows the interim acceptable limit for MNP as calculated for different rifampicin-containing regimens.

- HRZE (TB disease): 600 mg of rifampicin taken daily for six months (which equates to 1–12 months of total exposure).
- 4R (TB infection): 600 mg of rifampicin taken daily for four months (which equates to 1–12 months of total exposure).
- 3HR (TB infection): 75–300 mg of rifampicin taken daily for three months (which equates to 1–12 months of total exposure). This is the pediatric dosing schedule for 3HR.

The LTL approach would result in an interim AI-LTL of 8.5 ppm for 3HP. Instead of adopting the AI-LTL approach, the FDA and Sanofi agreed to a higher interim limit. Based on a benefit/risk assessment and an independent toxicology assessment, Sanofi proposed to the FDA that they would monitor the level of CPNP in rifapentine API and FPP batches with an interim limit ≤20 ppm at FPP release (i.e., when the product is released for sale onto the market) and 25 ppm at the end of the product shelf-life.

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 both the AI and the AI-LTL 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.

Table 3: Interim Acceptable Limit for MNP in Rifampicin-containing Regimens

| Regimen (indication) | Dose and duration of treatment | Calculation AI-LTL = AI * multiplier | AI-LTL | Calculation Interim acceptable limit in ppm = AI-LTL/MDD | Interim AI-LTL (ppm in API) |
|---|--|--------------------------------------|-------------|--|-----------------------------|
| 2(HRZE)/4(HR) (TB disease) | 600 mg daily for 6 months (>1-12 months of exposure) | 96 ng/day x 13.3 | 1280 ng/day | 1280 ng/600 mg | 2.1 ppm |
| 4R (TB infection) | 600 mg daily for 4 months (>1-12 months of exposure) | 96 ng/day x 13.3 | 1280 ng/day | 1280 ng/600 mg | 2.1 ppm |
| 3HR (TB infection) [calculated at pediatric doses] | 75-300 mg daily for 3 months (>1-12 months of exposure) | 96 ng/day x 13.3 | 1280 ng/day | 1280 ng/75 mg 1280 ng/300 mg | 17.1 ppm 4.3 ppm |

The WHO PQT/MED endorsed the FDA's proposed higher limits for rifapentine. The same 20-ppm interim limit applies to 3HP manufactured by Macleods as endorsed by the Global Fund.²⁴ Therefore, Sanofi and Macleods may resume drug release and distribution in compliance with this higher 20-ppm interim limit. The level of impurity must be reported for each batch of FPP at release and 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. This interim limit may change after the WHO PQT/MED and regulatory authorities finish reviewing the risk assessment reports submitted by rifampicin manufacturers at the end of 2020. In January 2021, the FDA published results from a laboratory analysis of MNP and CPNP content in rifampicin and rifapentine products. The tested rifampicin products all contained MNP levels below the 5 ppm interim limit. The one rifapentine product

tested (Sanofi) had CPNP levels between 8 and 15 ppm (under the interim 20 ppm limit).²⁵

5. Making sense of different risks

How does MNP exposure from rifampicin and CPNP exposure from rifapentine compare to background exposure to other N-nitrosamines? As shown in tables 4-6, the exposure to carcinogenic risk when taking 3HP or 1HP approximates one year of total background exposure to NDMA (from beverages and food, or air and water pollution). Exposure to nitrosamines when taking rifapentine²⁵ in the HPZM/Study 31/A5349 regimen is equivalent to eight years of total background exposure. These approximations assume that cancer risk with CPNP and MNP is equivalent to that with NDMA (in actuality, it may be less). Additionally, these approximations are calculated using the higher interim limits of 20 ppm for CPNP and 5 ppm for MNP. Over time, manufacturers will work to reach lower nitrosamine exposure levels as part of remediation plans.

Table 4: Estimated Food and Total Background Exposure to NDMA

| Source of NDMA exposure | Estimated exposure in ng/day | Estimated annual exposure in µg ^α |
|--|------------------------------|--|
| Processed meats in adults in EU ^β (lifetime daily) | 25 to 85 | 9 to 31 |
| Total mean background exposure ^χ (lifetime daily) | 100 to 1000 | 36.5 to 365 |

α. 1000 ng (nanograms) = 1 µg (microgram).

β. 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 Journal. 2017;15(6):e04786. doi: 10.2903/j.efs.2017.4786.

χ. Total background from contaminated beverages and food, air and water pollution. Source: Keszei A, 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: 10.13945/ajcn.112.043885.

Table 5: CPNP Exposure from Rifapentine-containing Regimens Compared to NDMA Background Exposure

| Regimen (indication) | Dose and duration of treatment | AI-LTL (in ppm) | Exposure with batch at AI-LTL ^α AI-LTL (ppm) * MDD * treatment days | Exposure with batches at FDA interim limit (20 ppm) 20 ppm * MDD * treatment days | Approximation to NDMA background exposure ^β equivalent with batches at 20 ppm |
|---|--|-----------------|---|---|---|
| 3HP (TB infection) | 900 mg weekly for 12 weeks = 12 days of treatment (<1 month of exposure) | 8.5 ppm | 8.5*900*12= 91.8 µg | 20*900*12= 216 µg | ~7 months of total background exposure |
| 1HP (TB infection) | 600 mg daily for 4 weeks = 28 days of treatment (<1 month of exposure) | 12.8 ppm | 12.8*600*28= 215 µg | 20*600*28= 336 µg | ~11 months of total background exposure |
| Rifaquin regimen (TB disease) | 600 mg twice weekly for 2 months, then 600 mg weekly for 4 months = 32 days of treatment (<1 month of exposure) | 12.8 ppm | 12.8*600*32= 246 µg | 20*600*32= 384 µg | ~1 year of total background exposure |

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| | | | | | |
|--|---|---------|--|--|---|
| 2(HPZM)/2(HPM) Study 31/A5349 regimen (TB disease) | 1200 mg daily for 4 months (>1-12 months of exposure) | 1.1 ppm | $1.1 \times 1200 \times 119 = 157 \mu\text{g}$ | $20 \times 1200 \times 119 = 2856 \mu\text{g}$ | ~8 years of total background exposure |
| 6P (TB infection) | 600 mg daily for 6 weeks then (>1-12 months of exposure) | 2.1 ppm | $2.1 \times 600 \times 42 = 53 \mu\text{g}$ | $20 \times 600 \times 42 = 504 \mu\text{g}$ | ~1 year and 4 months of total background exposure |

α. For calculation of AI-LTL values, see table 2.

β. NDMA background exposures calculated at 365 μg (see table 4).

Table 6: MNP Exposure from Rifampicin-containing Regimens Compared to NDMA Background Exposure

| Regimen (indication) | Current dose and duration of treatment | AI-LTL (in ppm) | Exposure with batch at AI-LTL ^α AI-LTL (ppm) * MDD * number of treatment days | Exposure with batch at FDA-agreed limit (5 ppm) 5 ppm * MDD * number of treatment days | Approximation to NDMA background exposure ^β equivalent with batches at 5 ppm |
|--|---|---------------------|--|--|---|
| 2(HRZE)/4(HR) (TB disease) | 600 mg daily for 6 months (>1-12 months of exposure) | 2.1 ppm | $2.1 \times 600 \times 182 = 229 \mu\text{g}$ | $5 \times 600 \times 182 = 546 \mu\text{g}$ | ~1 year and 6 months of total background exposure |
| 4R (TB infection) | 600 mg daily for 4 months (>1-12 months of exposure) | 2.1 ppm | $2.1 \times 600 \times 119 = 148 \mu\text{g}$ | $5 \times 600 \times 119 = 357 \mu\text{g}$ | ~1 year of total background exposure |
| 3HR (TB infection) [calculated at pediatric doses] | 75 mg daily for 3 months 300 mg daily for 3 months (>1-12 months of exposure) | 17.1 ppm 4.3 ppm | $17.1 \times 75 \times 91 = 117 \mu\text{g}$ $4.3 \times 300 \times 91 = 117 \mu\text{g}$ | $5 \times 75 \times 91 = 34 \mu\text{g}$ $5 \times 300 \times 91 = 136 \mu\text{g}$ | ~1 month ~4 months of total background exposure |

α. For calculation of AI-LTL values, see table 2.

β. NDMA background exposures calculated at 365 μg (see table 4).

6. Impact on TB drug supply

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

All batches of rifapentine released by Sanofi and Macleods will be 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 Global Fund Expert Review Panel (ERP).²⁸ The supply of rifapentine is expected to pick up substantially in 2021, with up to 3 million patient courses of 3HP available between Sanofi and Macleods.²⁹

In the event of rifapentine shortages or supply delays, TB programs may use alternative TPT regimens recommended by the WHO, including six, nine, or 36 months of isoniazid preventive therapy.

To date, there has been no observed impact on access to rifampicin. The WHO PQT/MED has not suspended any of the rifampicin prequalified APIs or medicines and has requested that all rifampicin API and medicines applicants test for MNP impurity in a representative number of batches.³⁰ The WHO PQT/MED expects to have all rifampicin results in the first quarter of 2021. For the few APIs for which manufacturers have already reported results, an interim limit of 5 ppm is being defined temporarily

for the impurity. The WHO PQT/MED is closely working with these companies to follow up on mitigation measures that should be applied as soon as possible, in order to decrease the impurity to lifetime acceptable levels.

Based on current guidelines, there is no recommended alternative to rifamycin-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.³¹

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 rifampicin and rifapentine products. For now, the rifapentine prices negotiated by Unitaid and its partners with Sanofi and Macleods remain in effect through 2021 for eligible countries.^{32,33} TB programs should remain vigilant for the possibility of higher rifapentine or rifampicin prices after 2021, and TB advocates and civil society should closely monitor global and local supply chains to avert shortages and stockouts of rifapentine and rifampicin.

7. The bottom line

Rifampicin and rifapentine remain essential medicines for the prevention and treatment of TB. The identification of N-nitrosamine impurities in rifampicin and rifapentine should not stop people from receiving TB treatment or preventive therapy. Health authorities have established temporary interim limits allowing manufacturers to distribute rifampicin FPP containing MNP at ≤ 5 ppm and rifapentine FPP containing CPNP at ≤ 20 ppm. Over time, manufacturers will need to reduce N-nitrosamine impurities to the respective AI limits of 0.16 ppm (for MNP) and 0.1 ppm (for CPNP). The AI-LTL limits calculated in tables 2 and 3 provide intermediary targets to track manufacturers' progress toward achieving the AI limits. All stakeholders invested in ending TB should work together to ensure the safety of, and public confidence in, TB medicines.

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.
- 2 International Agency for Research on Cancer. IARC monographs on the identification of carcinogenic hazards to humans [Internet]. (cited 2021 January 12.) <https://monographs.iarc.fr/list-of-classifications>.
- 3 Ibid.
- 4 European Medicines Agency. Assessment report: nitrosamine impurities in human medicines (EMA/369136/2020). Amsterdam: European Medicines Agency; 2020. <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities>.
- 5 Food and Drug Administration (U.S.). Statement on new testing results, including low levels of impurities in ranitidine drugs [Internet]. 2019 November 1 (cited 2021 January 12). <https://www.fda.gov/news-events/press-announcements/statement-new-testing-results-including-low-levels-impurities-ranitidine-drugs>.
- 6 Food and Drug Administration (U.S.). Laboratory analysis of ranitidine and nizatidine products [Internet]. 2019 November 1 (cited 2021 January 12). <https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-ranitidine>.
- 7 European Directorate for the Quality of Medicine. The EDQM's response to nitrosamine contamination [Internet]. (cited 2021 January 12). <https://www.edqm.eu/en/edqms-response-nitrosamine-contamination#Nitrosamine%20contamination%20in%20brief>.
- 8 World Health Organization. Information note: nitrosamine impurities. Geneva: World Health Organization; 2019. https://www.who.int/medicines/publications/drugalerts/InformationNote_Nitrosamine-impurities/en/.
- 9 European Medicines Agency. Nitrosamine impurities [Internet]. (cited 2021 January 12). <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities>.
- 10 Food and Drug Administration (U.S.). Control of nitrosamine impurities in human drugs: guidance for industry. Rockville, MD: Food and Drug Administration; 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs>.
- 11 World Health Organization. WHO prequalification unit—medicines request to manufacturers to conduct risk assessments to evaluate the potential for the presence of nitrosamine impurities [Internet]. 2020 April 2 (cited 2021 January 12). <https://extranet.who.int/pqweb/news/manufacturers-conduct-risk-assessments>.
- 12 World Health Organization. Nitrosamine concerns for rifapentine and rifampicin: update and FAQs [Internet]. 2020 December 18 (cited 2021 January 12). https://extranet.who.int/pqweb/sites/default/files/documents/FAQ_Nitrosamine_18Dec2020.pdf.
- 13 Ibid.
- 14 Ibid.
- 15 For a list of rifampicin manufacturers, search for rifampicin under the World Health Organization's finished pharmaceutical products list, available at: <https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products>. Additional rifampicin manufacturers may be listed on the Global Fund medicines eligible product list, in the UK Electronic Medicines Compendium, or in the FDA drugs database, among other sources.
- 16 World Health Organization. Nitrosamine concerns for rifapentine and rifampicin.
- 17 Ibid.
- 18 European Medicines Agency. ICH M7 assessment and control of DNA (reactive) mutagenic impurities in pharmaceutical to limit potential carcinogenic risk. Amsterdam: European Medicines Agency; 2018. <https://www.ema.europa.eu/en/ich-m7-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential#current-effective-version--section>.
- 19 The N-nitrosamines with a TD50 below 1.5 mg/kg/day belong to the “cohort of concern” as defined in ICH M7(R1) and are NMPEA, NDEA, NDMA, NMEA, NNN, NMOR, NMA, NDPA, NDPA, NDPA, NDPA, NPYR, MNNG, NMBA, and NPIP. CPNP and MNP are not listed in the cohort of concern. Consequently, the FDA took the TD50 of NDMA to calculate the AI for CPNP.
- 20 Helguera AM, Cordeiro MMDS, Cabrera Perez MA, Combes RD, Gonzalez MP. Quantitative structure carcinogenicity relationship for detecting structural alerts in nitroso-compounds; Species: Rat; Sex: Male; Route of administration: Water. *Toxicol Appl Pharmacol.* 2008;231(2):197–207. doi: 10.1016/j.taap.2008.04.008.
- 21 DeBellas, Carmen (Food and Drug Administration Division of Regulatory Operations and Infectious Diseases, Rockville, MD). Personal communication with: Sandrine Cloëz (on behalf of Treatment Action Group, New York, NY). 2020 December 18.
- 22 European Medicines Agency. ICH M7 assessment and control of DNA (reactive).

- 23 Food and Drug Administration (U.S.). FDA works to mitigate shortages of rifampin and rifapentine after manufacturers find nitrosamine impurities [Internet]. 2020 October 9 (cited 2021 January 12). <https://www.fda.gov/drugs/drug-safety-and-availability/fda-works-mitigate-shortages-rifampin-and-rifapentine-after-manufacturers-find-nitrosamine>.
- 24 Global Fund. Result of the quality risk assessment review of Isoniazid/Rifapentine 300mg/300mg film-coated tablets by the ERP [Letter]. 2020 December 16. [On file with Treatment Action Group.]
- 25 Food and Drug Administration (U.S.). Laboratory analysis of rifampin/rifapentine products [Internet]. 2021 January 28 (cited 2021 February 18). <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamines-rifampin-and-rifapentine>.
- 26 Ibid.
- 27 European Medicines Agency. Nitrosamine impurities.
- 28 Global Fund. List of tuberculosis pharmaceutical products classified according to the Global Fund Quality Assurance Policy [Internet]. 2020 July 6 (cited 2021 January 20). https://www.theglobalfund.org/media/4757/psm_productstb_list_en.pdf?u=637319006341100000.
- 29 IMPAACT4TB (Press Releases). New patient-friendly tuberculosis preventive therapy to be rolled out in five high-burden TB countries at affordable price. 2 February 2021 (cited 3 February 2021). <https://www.impaact4tb.org/>.
- 30 World Health Organization. Nitrosamine concerns for rifapentine and rifampicin.
- 31 World Health Organization. Information note: nitrosamine impurities.
- 32 Unitaid, The Global Fund, Stop TB Partnership. Rifapentine global price discount [Internet]. 2019 November 1 (cited 2021 January 9). <https://www.impaact4tb.org/communique-rifapentine-global-price-discount/>.
- 33 Unitaid. Rifapentine/isoniazid 300mg/300mg global price announcement. [On file with Treatment Action Group.]