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FAQ

Nitrosamines and TB Medicines: What People Taking TB Treatment or TB Preventive Treatment Need to Know

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If you are reading this guide, you may have recently received a diagnosis of drug-susceptible tuberculosis (TB) and are now preparing to start your treatment. Similarly, you may be taking medicine to protect yourself from developing TB disease. This type of treatment is called TB preventive treatment (sometimes called TPT). TB preventive treatment protects people who are already infected with the TB bacterium from falling ill with TB disease, and it shields people who are uninfected but at risk of TB exposure from getting infected.

The drugs used to treat TB have been in use for decades and are well understood by health care workers and scientists. It is not an exaggeration to say that hundreds of millions of people have received these drugs over time. Recently, health authorities and drug manufacturers have identified a type of chemical impurity called nitrosamines in some TB medicines. This document answers frequently asked questions about nitrosamines for people taking TB treatment or TB preventive treatment.



What are nitrosamines?

Nitrosamines are common chemicals found in water and foods including cured and grilled meats, dairy products, and vegetables. Everyone is exposed to some background level of nitrosamines in daily life.

In recent years, health authorities and drug manufacturers have identified nitrosamines in several categories of drugs, including in two medicines used to treat TB: rifapentine and rifampicin. The presence of nitrosamines in medicines is considered an impurity, so drug makers are now working with health authorities to reduce the level of nitrosamines in pharmaceutical products.

There are different types of nitrosamines. The nitrosamine found in rifapentine is called CPNP and the impurity in rifampicin is called MNP.

Why is the presence of nitrosamines in medicines a concern?

Nitrosamines are possible human carcinogens. This means that they may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time (decades). TB treatment is taken for a short period of time — usually for six months, and sometimes for nine months or up to one year. Similarly, TB preventive treatment using rifapentine or rifampicin is also taken for a short period of time — anywhere from one month to four months.

Health authorities in the European Union, United States, and Canada have assessed the risk of nitrosamines in medicines and have stated that there is a very low risk that nitrosamine impurities at the levels found in TB drugs and other medicines could cause cancer in humans.

What is the link between nitrosamines and cancer?

Most knowledge about nitrosamines and cancer risk comes from studies in animals. For certain types of nitrosamines, there is also evidence from epidemiological studies (for example, studies where people are followed for years or even decades, during which time researchers document their exposure to nitrosamines and look for the occurrence of any cancers). The nitrosamines identified in rifapentine and rifampicin (CPNP and MNP) are believed to be less carcinogenic than other known types of nitrosamines (based on an analysis of chemical structure).

Why are nitrosamines present in medicines?

Nitrosamine impurities can form in some medicines during manufacturing. They can also appear when drugs expire or outlive their shelf life.

Most medicines do not contain nitrosamines, and these impurities should be avoided whenever possible. Where nitrosamines are present in medicines, they should be controlled below a level where human cancer risk associated with exposure is considered negligible (small enough to be considered insignificant). Nitrosamines appear in rifapentine and rifampicin because of their innate chemical structure. That means that all manufacturers of rifapentine and rifampicin will need to take steps to control the development of nitrosamines during manufacturing.

Are nitrosamines in TB medicines a new concern?

No. Nitrosamine impurities in medicines, generally, and TB drugs, specifically, are not new. Rather, health authorities and manufacturers have recently recognized the issue and have acted to document and reduce the level of nitrosamines in medicines.

Which TB treatment regimens are affected?

Two TB drugs contain nitrosamines: rifapentine and rifampicin. Both rifapentine and rifampicin are important drugs for the treatment of TB and are usually used in the following two regimens:

- The **HRZE** regimen: this is the standard six-month TB treatment regimen and 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. This is the regimen most people with drug-sensitive TB receive.
- The **HPZM** regimen: this is a new four-month regimen and 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. In 2020, researchers at the U.S. Centers for Disease Control and Prevention (CDC) completed a phase III clinical trial showing that this four-month HPZM regimen based on rifapentine is as effective at curing TB as the standard six-month HRZE regimen. The World Health Organization and the CDC both recommend the HPZM regimen as an alternative to the standard six-month HRZE regimen, meaning that four-month TB treatment will become more common over the coming years.

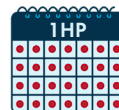
Which TB preventive treatment regimens are affected?

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).



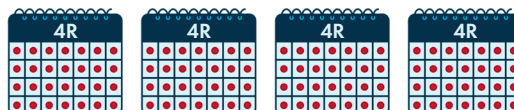
Which TB preventive treatment regimens are affected? (continued)

Rifampicin is 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.

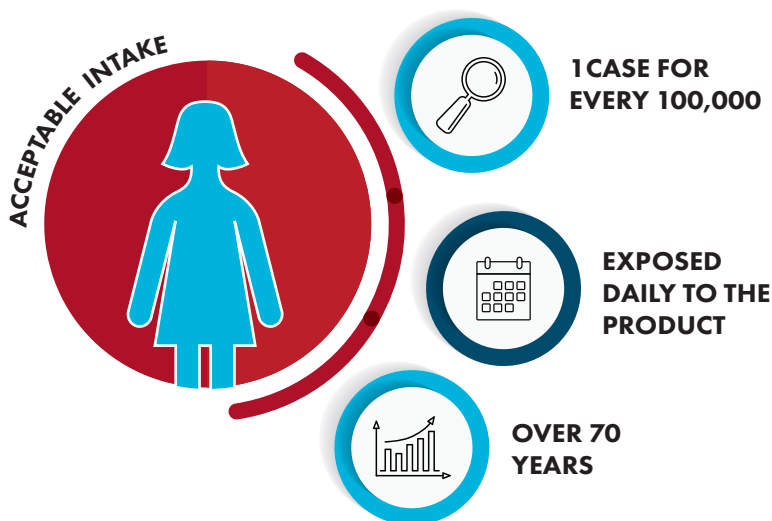


What risk am I exposed to when taking TB treatment or TB preventive treatment containing nitrosamines?

Ingesting low levels of nitrosamines is not expected to cause harm. Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time.

To ensure that the risk of cancer remains low, regulatory agencies such as the FDA have established “acceptable intake” limits for nitrosamines in medicines. In order to distribute medicines, drug manufacturers must demonstrate that the level of nitrosamines does not exceed these limits. The acceptable intake limit represents a negligible risk of cancer (1 in 100,000) assuming a person is exposed to nitrosamines daily for a period of 70 years.

Higher limits are allowed for medicines that are taken for a shorter duration than 70 years or less frequently than daily. This includes TB treatments and medicines used for TB preventive treatment, which are not taken for life. TB treatment using the HRZE regimen usually lasts six months. In the future, more people will receive a four-month treatment course using HPZM. TB preventive treatment regimens based on rifampicin or rifapentine range from one to four months in duration. In the case of the 3HP regimen, medicines are taken once a week, rather than daily.



How do nitrosamines in TB medicines compare to other exposures?

Everyone has some background exposure to nitrosamines. Exposure to nitrosamines in daily life varies widely depending on where a person lives, what a person eats, and other environmental factors. Generally speaking, the **exposure to nitrosamines from taking a full course of the HRZE regimen equates to approximately a year or more of usual background exposure expected in daily life.** The exposure is higher for the HPZM regimen, somewhere around eight years of usual background exposure expected in daily life.

Further, **exposure to nitrosamines from taking a TB preventive treatment regimen containing either rifapentine or rifampicin is approximately a year or less of usual background exposure in daily life.**

These exposures were calculated assuming that the CPNP and MNP impurities in rifapentine and rifampicin are similar to other types of nitrosamines found in foods and the environment that are carcinogenic. CPNP and MNP may be less carcinogenic than these other nitrosamines, so the risk of cancer from taking TB treatment or TB preventive treatment may be even lower.

Are there different risks for children and pregnant people?

The same acceptable intake limits for nitrosamines in adults set by the FDA also apply to children. Children who take TB treatment or TB preventive treatment are not believed to be at any higher risk of developing cancer from nitrosamine exposure than adults.

TB in pregnancy poses a serious risk to both mother and fetus and must be treated. Some nitrosamines have the potential to cause birth defects. The risk of nitrosamine-related birth defects is much lower than the risks of untreated TB in pregnancy (which can lead to poor pregnancy outcomes and jeopardize the health of both mother and infant). It is not known whether the nitrosamines in rifapentine and rifampicin (CPNP and MNP) increase the risk of birth defects. Pregnant women with TB should continue to take TB treatment under the close management of their health care providers.

Pregnant women at risk of TB may take alternative TB preventive treatment regimens that do not contain nitrosamines (one option is called isoniazid preventive therapy) or choose to take TB preventive treatment at the end of pregnancy (after delivery). Encouragingly, one study found that rates of TB among mothers and infants were no higher among women who waited until after delivery to start TB preventive treatment, compared with individuals who started it during pregnancy. Pregnant individuals should consult their health care providers about which TB preventive treatment regimen to take and when to begin treatment (before or after delivery).

Can I treat TB with a drug regimen that does not contain rifapentine or rifampicin?

Currently, all regimens recommended to treat drug-susceptible TB involve either rifapentine or rifampicin.

Can I take a TB preventive treatment regimen that does not contain rifapentine or rifampicin?

Yes. Isoniazid preventive therapy (IPT) is an effective regimen for preventing TB infection and contains only the drug isoniazid (not rifapentine or rifampicin). If you feel uncomfortable taking a TB preventive treatment regimen with rifapentine or rifampicin, you can ask a health care provider if IPT is available in your area. The 6H and 9H regimens (6 months and 9 months of isoniazid preventive therapy, respectively) are not affected by nitrosamine impurities. However, before starting IPT, you should know that the treatment duration will be longer (at least six months) and that it may carry a higher risk of liver damage than the shorter TB preventive treatment regimens based on either rifapentine or rifampicin. These trade-offs may be acceptable for some people but not others.

Have TB medicines with nitrosamines been recalled?

Yes. In October 2022, a manufacturer recalled bottles of rifampicin capsules for exceeding the acceptable limit of MNP. **Health authorities now require manufacturers of rifampicin and rifapentine to systematically test each batch of drugs made to ensure that the level of nitrosamines does not exceed the established limit.** Any batches found to contain a level of nitrosamine over the limit should not be distributed to patients.

Should I stop taking my TB treatment or TB preventive treatment if it includes a medicine known to contain nitrosamines?

No, do not stop taking your TB treatment or TB preventive treatment unless advised to by a health care provider. TB is a life-threatening disease but is curable when treatment is taken as prescribed. The known risks of TB far outweigh the theoretical risks of cancer associated with nitrosamines. Moreover, because of the actions taken by health authorities and manufacturers, your TB medicines contain nitrosamines at or below the established intake limits. A person who takes a drug that contains nitrosamines at or below these limits every day for the duration of treatment is not expected to have an increased risk of cancer.

If you have any concerns about the safety of your TB treatment, consult a health care provider.

If, after considering all the available information, you feel uncomfortable taking a TB preventive treatment regimen containing rifapentine or rifampicin, then you may choose to take isoniazid preventive therapy instead. If you have any concerns about the safety of your TB preventive treatment regimen, consult a health care provider. TB preventive treatment remains one of the best ways to keep yourself and your family safe from TB, which in turn will help your community become — and remain — TB free.

Are there ways I can reduce my intake of other nitrosamines when taking TB treatment or TB preventive treatment?

Yes. You can take action to reduce the level of nitrosamines you are exposed to in daily life by avoiding tobacco or by eating fewer grilled or preserved (e.g., cured, smoked) meats. While individuals can take meaningful action in this regard, controlling nitrosamines ultimately depends on government monitoring and removing these chemicals from foods, water, and medicines.

Where can I find more information on nitrosamines?

You can consult the following resources for additional information on nitrosamines and TB medicines. The first document listed contains citations and references for the technical and scientific information on nitrosamines included in this document.

- IMPAACT4TB. Information Note: N-nitrosamines and Tuberculosis Medicines Rifapentine and Rifampicin. New York: Treatment Action Group; March 2023. https://www.treatmentactiongroup.org/wp-content/uploads/2023/04/04_23_nitrosamine_technical_brief_final.pdf.
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- World Health Organization. Nitrosamine concerns for rifapentine and rifampicin: update and FAQs [Internet]. 2020 December 18. <https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifapentine-and-rifampicin-update-and-faqs>.
- Centers for Disease Control and Prevention (U.S.). Update on rifamycin issues [Internet]. 2020 September 14. https://www.cdc.gov/tb/publications/letters/Rifamycin_Update.html.