

FAQ

Nitrosamines and TB Medicines: What People Taking TB 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. 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.

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: rifampicin and rifapentine. 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 rifampicin is called MNP and the impurity in rifapentine is called CPNP.

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.

Health authorities in the European Union, United States, and Canada, in particular, 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 rifampicin and rifapentine (MNP and CPNP) 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 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).

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 taken action to document and reduce the level of nitrosamines in medicines.

Which TB treatment regimens are affected?

Two TB drugs contain nitrosamines: rifampicin and rifapentine. Both rifampicin and rifapentine 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, 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, moxifloxacin) for two months followed by two months of rifapentine, isoniazid, and moxifloxacin. 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. Health authorities, including the CDC and the World Health Organization, are now reviewing the safety and efficacy of the HPZM regimen and may recommend its use soon.

What risk I am exposed to when taking TB 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 (1:100,000) 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 medicines, which are not taken for life. TB treatment using the HRZE regimen usually lasts six months. In the future, some people may receive a four-month treatment course using HPZM.

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, **exposure to nitrosamines from taking a full course of the HRZE regimen is approximately a year or more of usual background exposure in daily life.** The exposure is higher for the HPZM regimen, somewhere around 10 years of the background exposure expected 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 actual exposures from taking TB treatment may be even lower.

Are there different risks for children and pregnant women?

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

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

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

Have TB medicines with nitrosamines been recalled?

No. Until now, health authorities and drug manufacturers have not recalled any TB medicines due to nitrosamine impurities. **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 over the limit should not be distributed.

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

No, do not stop taking your TB treatment. 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.

Are there ways I can reduce my intake of other nitrosamines when taking TB 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 meats. While individuals can take meaningful action in this regard, controlling nitrosamines ultimately depends on governments 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:

- Treatment Action Group. Information Note: N-nitrosamines and TB medicines. New York: Treatment Action Group; February 2021. <https://www.treatmentactiongroup.org/publication/nitrosamines-and-tb-medicines-information-note-and-patient-faqs>
- Food and Drug Administration. FDA updates and press announcements on nitrosamines in rifampin and rifapentine. 2021 January 21. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamines-rifampin-and-rifapentine>.
- World Health Organization. Nitrosamine concerns for rifapentine and rifampicin: update and FAQs. 2020 December 18. <https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifapentine-and-rifampicin-update-and-faqs>.
- Centers for Disease Control and Prevention. Update on rifamycin issues. 2020 September 14. https://www.cdc.gov/tb/publications/letters/Rifamycin_Update.html.