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Treatment Action Group

FAQ

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

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If you are reading this guide, you may be taking medicine to protect you from developing tuberculosis (TB) disease. This type of treatment is called TB preventive therapy, or TPT for short. TPT 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 in the first place. The drugs used to prevent 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 tens 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 TPT.

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 prevent 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 preventive treatment involving rifapentine or rifampicin is taken for a short period of time—anywhere from one month to four months.

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 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).

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 preventive treatment regimens are affected?

Two TB drugs contain nitrosamines: rifampicin and rifapentine.

Rifampicin is used in two recommended TPT regimens:

- **3HR:** rifampicin and isoniazid taken daily for three months.
- **4R:** rifampicin taken daily for four months.

Rifapentine is used in two recommended TPT regimens:

- **3HP:** rifapentine and isoniazid taken once a week for 12 weeks (three months).
- **1HP:** rifapentine and isoniazid taken daily for four weeks (one month).

What risk I am exposed to when taking TB preventive therapy 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 U.S. Food and Drug Administration (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 medicines used for TB preventive therapy. TPT 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, **exposure to nitrosamines from taking a TPT 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. CPNP and MNP may be less carcinogenic than these other nitrosamines, so the actual exposures from taking TPT 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 a TPT regimen containing nitrosamines are not believed to be at any higher risk of developing cancer than adults.

Some nitrosamines have the potential to cause birth defects. It is not known whether the nitrosamines in rifapentine and rifampicin (CPNP and MNP) increase the risk of birth defects. Pregnant women at risk of TB may take alternative TPT regimens that do not contain nitrosamines (one option is called isoniazid preventive therapy) or choose to take TPT 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 TPT compared with individuals who started TPT during pregnancy. Pregnant individuals should consult their health care provider about which TPT regimen to take and when to begin treatment (before or after delivery).

Can I take a TPT regimen that does not contain rifampicin or rifapentine?

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

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 preventive therapy if it includes a medicine known to contain nitrosamines?

No, do not stop taking your TB preventive treatment unless advised to by a health care worker. The risks of developing TB far outweigh the theoretical risks of cancer associated with nitrosamines. Moreover, because of the actions taken by health authorities and manufacturers, your TPT regimen contains nitrosamines at or below the established intake limits and therefore poses only a negligible risk of cancer.

If after considering all of the available information you feel uncomfortable taking a TPT regimen containing rifampicin or rifapentine, then you may choose to take IPT instead. If you have any concerns about the safety of your TPT regimen, consult a health care provider.

TB is a life-threatening infectious disease, and TPT 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 TPT?

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 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; 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.