

## A Measure of Resistance

### Detecting Tamiflu Metabolite in Sewage Discharge and River Water

During the flu season each year, combating the different strains of the influenza virus becomes a public health priority, with treatment dependent upon two groups of antiviral drugs: neuraminidase inhibitors and M2 ion channel inhibitors. Oseltamivir phosphate, marketed as Tamiflu, is a popular neuraminidase inhibitor widely used to treat flu symptoms. Oseltamivir carboxylate (OC), Tamiflu's active metabolite, is known to withstand activated sludge treatment at sewage treatment plants (STPs), but less is known about how much OC may make its way into waterways that receive STP effluent. Now a new study conducted in Kyoto City, Japan,

Resistance in the making? Potential influenza A host meets potential source of active Tamiflu metabolite



## No Small Worry

### Airborne Nanomaterials in the Lab Raise Concerns

The use of engineered nanomaterials has grown dramatically over the past decade as the pharmaceutical, electronics, and other industries leverage these materials' unique physical and chemical properties. In environmental circles, nanomaterials have aroused concern because, even as their use burgeons, their impact on animal and plant life remains largely unknown. Moreover, scientists studying the environmental effects of nanomaterials might unknowingly be putting their own health at risk [EHP 118:49–54; Johnson et al.].

The National Institute for Occupational Safety and Health, which conducts research on workplace safety, has no recommended exposure limit guidelines for nanomaterials, and the Occupational Safety and Health Administration has no permissible exposure limit specific to engineered nanomaterials. However, recent animal toxicology studies suggest nanomaterials may cause specific adverse health effects. For example, carbon nanotubes have been shown to induce inflammation and oxidative stress in animal models.

To assess the magnitude of potential exposure in a laboratory setting, a team of researchers measured the amount of carbonaceous nanomaterials (CNMs) released into the air during routine material handling and processing tasks in standard environmental matrices such as artificial river water. The authors evaluated nanomaterial releases using real-time particle counters and transmission electron microscopy.

during the 2008–2009 flu season reports some of the first measurements of OP occurrences in STP discharge and in river water [EHP 118:103–107; Ghosh et al.].

According to the World Health Organization, between 250,000 and 500,000 people die each year from influenza, and each year, millions of people take Tamiflu to battle flu symptoms. After the sewage treatment process, the excreted active metabolite remains in STP effluent and travels to waterways where effluent is discharged.

The investigators in the current study collected samples from STP effluent and from river water on three different occasions: at the beginning of the flu season, during the peak period, and 2 weeks after the peak period. Using solid-phase extraction followed by liquid chromatography–tandem mass spectrometry, they measured the highest concentration of OC, 293.3 ng/L, in an STP discharge sample collected during the peak of the flu season. Concentration amounts were higher in effluent from STPs that used traditional activated sludge treatment; in contrast, effluent from plants that used advanced ozonation as tertiary treatment contained significantly lower OC levels (37.9 ng/L). River water samples showed a range of OC levels from 6.6 to 190 ng/L during the peak of the flu season.

Previous research indicates OC concentrations ranging from 80 to 230 ng/L will disable 50% of the influenza virus. This level of exposure is most likely to kill virus particles that are particularly susceptible to OC, while selecting for viruses that are resistant to the drug's effects. The authors note, "During a common flu season, waterfowl can ingest large quantities of OC with virus. . . . Exposing waterfowl infected with influenza A virus to elevated levels of OC in open waterways could trigger the development of Tamiflu-resistant viral strains."

The authors suggest ozonation as tertiary treatment that may reduce OC load in STP effluent. They also recommend conducting further investigations to determine the fate of antiviral drugs at every interval of the STP process.

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The research team found that CNMs became airborne when they were handled and weighed in the lab. Smaller structures, with an aerodynamic diameter of less than 1  $\mu\text{m}$ , scattered more readily than larger particles.

A surprise finding was the substantial release of CNMs during sonication, a common laboratory process used to break apart agglomerates of nanomaterials into aqueous dispersions. Sonication produced a CNM-containing mist that could be inhaled by workers or that could leave CNMs on laboratory surfaces after the water evaporated. The extent of release during sonication was increased when natural organic matter was added to the solution, as is often done to simulate conditions in the environment. Hydrophobic CNMs exhibited higher airborne particle number concentrations during handling than during sonication, whereas hydrophilic CNMs exhibited the opposite trend.

These findings contradict the belief that risks of exposure are minimized when working with nanomaterials in liquid suspensions. The authors believe this field case study is the first to demonstrate the release of CNMs during sonication and also the first to detail nanomaterial release in an environmental laboratory. They caution that more robust statistically based experimental research is needed to evaluate CNM exposure among laboratory workers. Until then, they urge researchers working with nanomaterials to use appropriate personal protective equipment in the laboratory and to adopt adequate engineering controls to minimize their exposure.

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## Critical Confluence

### Gene Variants, Insecticide Exposure May Increase Childhood Brain Tumor Risk

Epidemiologic data have suggested a link between pesticide exposures and childhood brain tumors. The link may be specific to insecticides such as organophosphorus and carbamate compounds, which are known to target the nervous system. Previously published work [*EHP* 113:909–913] investigated the role of individual genetic variation with a focus on paraoxonase (PON1), a key enzyme in the metabolism of organophosphorus insecticides commonly used in homes at the time but now banned for residential use. This work showed that children with brain tumors were more likely to carry a common single-nucleotide polymorphism (SNP) gene variant in the promoter region of the *PON1* gene (*PON1*<sub>C-108T</sub>) than other children, and that the association between this SNP and brain tumors was stronger in children with a history of home insecticide exposure. Research in an expanded study population now provides additional evidence that exposure to insecticides, paired with specific metabolism gene variants, may increase the risk of childhood brain tumors [*EHP* 118:144–149; Searles Nielsen et al.].

The research population included 201 children in California and Washington who had been diagnosed with a primary tumor of the brain, cranial nerves, or meninges between 1984 and 1991, as well as 285 children from the same geographic areas who served as controls. All children were aged 10 years or younger. Genetic information was extracted from archived dried blood spots used for routine screening

tests when the children were born. In addition to *PON1*<sub>C-108T</sub>, the genetic analysis covered 7 other gene polymorphisms that might influence the children's ability to metabolize insecticides. Interviews with the children's mothers provided data on prenatal and childhood exposures to insecticides in the home.

Between the cases and controls, there was little difference in the prevalence of any of the polymorphisms. For cases, more of the mothers reported in-home insecticide use during pregnancy, but in-home treatment during childhood was more common among controls. Data analysis confirmed the original observation that children exposed to insecticides were more likely to have brain tumors if they also carried the *PON1*<sub>C-108T</sub> SNP. Evidence of similar interactions also were observed with two other gene variants, *FMO1*<sub>C-9536A</sub> and *BCHE*<sub>A539T</sub>, which also may affect the ability to detoxify organophosphorus and/or carbamate insecticides.

These findings suggest that children who are exposed to insecticides at a young age may have a greater risk of developing brain tumors if they carry these and possibly other polymorphisms. Larger studies are needed to confirm the findings, and environmental and biological measurements of specific pesticides, inclusion of more polymorphisms, and detailed information on exposure timing and dose would strengthen support for causal effects of insecticides and gene–environment interactions on the risk of childhood brain tumors.

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## When to Warn?

### Comparing Heat Indices to Evaluate Public Health Risks

Summer heat waves can be deadly, particularly for vulnerable populations such as the elderly. Prior to a heat wave's arrival many cities warn their residents to take precautions such as making sure they drink enough water. But what are the best criteria for issuing a warning of an impending heat wave? A team of scientists from the New York City Department of Health and New York University Medical School compared different metrics used to predict these potentially lethal events [*EHP* 118:80–86; Metzger et al.]. They found that New York City's current method of basing advisories on the maximum heat index provided a realistic prediction of mortality risk during hot weather.

New York City is one of several places where alerts of excessive heat are triggered by rises in the maximum heat index, a combination of heat and humidity conditions that are forecast for the succeeding 24–48 hr. Alerts typically are issued when the maximum heat index is forecast to exceed 100–105°F (depending on location); some meteorological judgment can be applied by National Weather Service regional staff in whether to issue a heat alert.

In other cities, alerts are triggered by certain spatial synoptic classification (SSC) categories. Under the SSC system, the dominant local weather pattern is categorized into one of several types depending

on temperature, dew point, wind direction, wind speed, and cloud cover, as measured four times daily. The SSC categories classified as potentially dangerous weather patterns are determined for a local area by calculating the historical number of deaths in the local region associated with those weather patterns.

The researchers evaluated models using the maximum heat index, the SSC, and maximum, minimum, and average temperatures to predict heat wave deaths in New York City between 1997 and 2006.

They found the National Weather Service maximum heat index provided the most reliable prediction of heat-related deaths as confirmed by mortality data from the city's Office of Vital Statistics, with a spike in the magnitude of the heat–mortality association at maximum heat indices of 95–100°F. Using more variables such as wind speed and precipitation in forecasting heat waves improved the predictive models slightly but also complicated the task of translating complex forecasts into meaningful public health messages.

The authors conclude New York City officials should continue to issue heat alerts when the maximum heat index is forecast to exceed 95–100°F. They also say that repeated warnings should be issued throughout the heat wave and as the maximum heat index increases. Before other cities adopt use of the maximum heat index, however, they should conduct their own analyses with local data.

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New York City heat wave, 2 August 2006

