

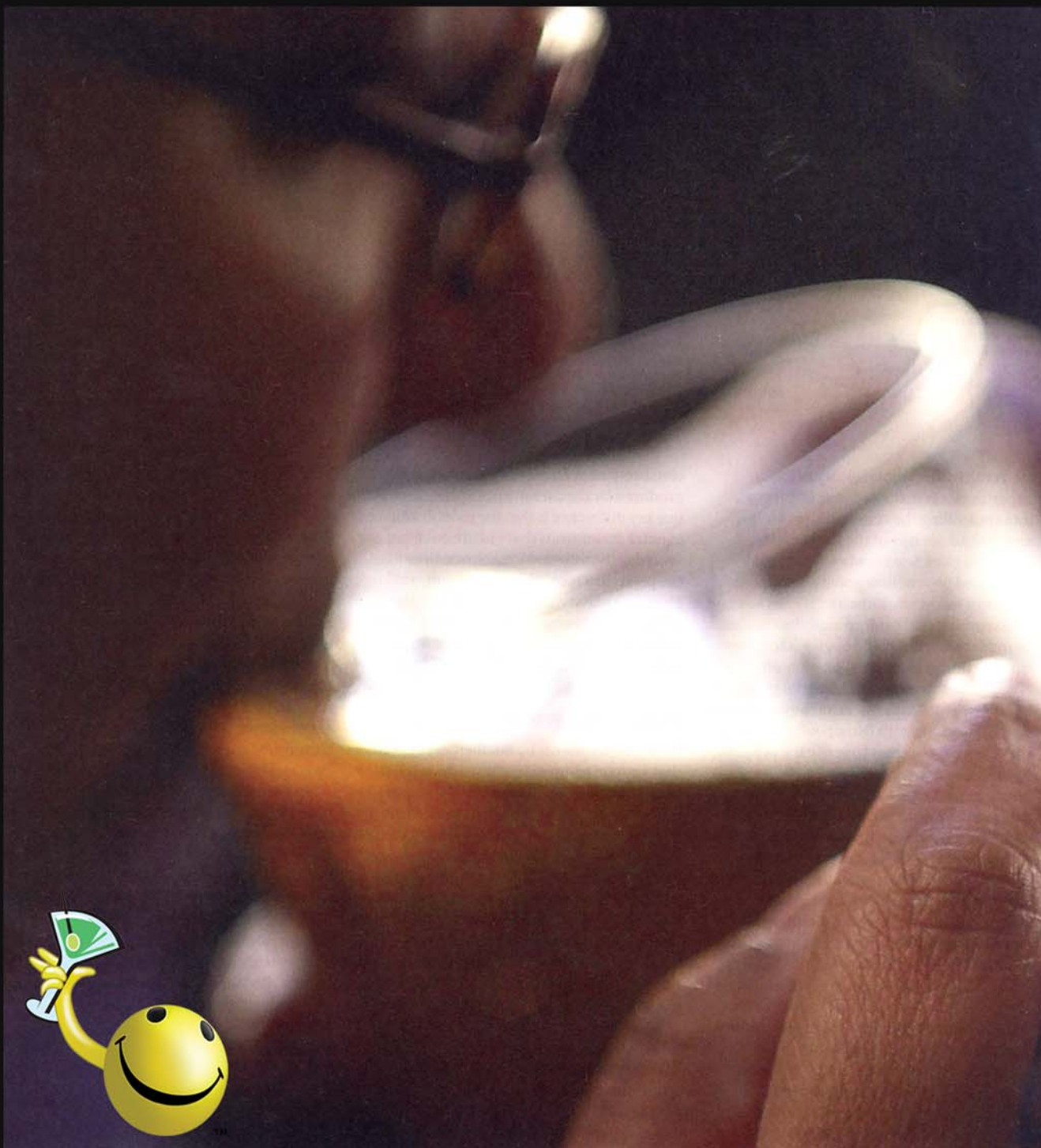
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What's your poison?

Could the damage wreaked by alcohol, tobacco, pollution and a bad diet all be caused by the same little molecule? By Lisa Melton



little molecule, asks Lisa Melton



Alcohol and smoke are major sources of the potent toxin acetaldehyde

IT'S HARD to look fetching with a hangover. Curtains closed, you lie in bed with a parched mouth, pounding head and queasy stomach. On your way to the kitchen for a glass of water you catch sight of yourself in a mirror. Not a pretty sight. And if you could witness the state of your insides you'd be even more horrified.

You are probably blaming your haggard state on dehydration, or impurities in whatever it was you drank last night, but you're only partly right. Another big reason for your hangover is a simple molecule called acetaldehyde, produced by your liver as it breaks down ethanol. You can take comfort from the fact that once the acetaldehyde has cleared from your system you will feel a lot better, but your internal organs aren't so lucky. They will be feeling the effects of acetaldehyde for much longer.

For a long time, acetaldehyde was thought to be a harmless intermediate in the breakdown of ethanol and was pretty much ignored. Then its sinister edge began to emerge. It started in the 1980s when alcohol researcher Victor Preedy of King's College London found that acetaldehyde is a powerful muscle poison, roughly 30 times more toxic than ethanol itself.

It has since become clear that acetaldehyde is the real demon in the demon drink. For 30 years researchers have known that excessive alcohol intake causes serious long-term damage to virtually every internal organ: brain, kidneys, gonads, skeletal muscle, liver, heart, uterus and digestive system. The assumption was that ethanol itself was to blame, but the mechanism was unclear. Now, as we find out more about how drink wreaks long-term havoc, the spotlight is increasingly moving away from ethanol and towards acetaldehyde.

It's not just our boozing habits that are to blame. Tobacco smoke, exhaust fumes and foods all contribute to your acetaldehyde load. The bacteria living in your mouth and guts churn it out in bucket loads. The onslaught on your body comes from within and without.

Measuring overall acetaldehyde exposure is tricky as the molecule is quickly broken down in the body, but researchers now believe that acetaldehyde is at least partly responsible for the rising incidence of cancer and liver disease as well as, possibly, Alzheimer's.

For such an innocuous-looking molecule, acetaldehyde is surprisingly toxic. "With the kind of levels we take in, most of us should be dead," says Richard Deitrich, a pioneer in acetaldehyde research at the University of Colorado Alcohol Research Center in Aurora. Fortunately, the body has a battery of detoxifying enzymes that specialise in breaking the stuff down.

Almost every tissue in the body is equipped with the enzymes known as aldehyde dehydrogenases (ALDHs), which convert acetaldehyde to harmless acetic acid. There are 19 different ALDHs in humans but one in particular, ALDH2, does most of the work – especially in the liver.

As soon as you start drinking alcohol, your liver revs into action. First, it converts the ethanol into acetaldehyde using another enzyme, alcohol dehydrogenase.

Acetaldehyde is then broken down by ALDH2 and the resulting acetic acid is burned as fuel in the muscles. **The liver does a fantastic job: normally it eliminates over 99 per cent of the acetaldehyde. Only minute amounts escape into the bloodstream. But that's where the problems start.**

The average liver can process about 7 grams of ethanol an hour – though in heavy drinkers that figure can rise to 10 grams – meaning that

Skeletal muscle is particularly badly affected. Preedy has found that rats given a single dose of ethanol end up with significant muscle damage as a result of acetaldehyde attacking proteins. The changes persist for more than 24 hours, long after the chemical itself has disappeared from the system (*Alcohol and Alcoholism*, vol 40, p 485). “It’s a common misconception that the brain and the liver are the two organs most affected by alcohol abuse,” says Preedy. “Muscle damage is the most common.” Among alcoholics, he says, muscle damage is five times more common than cirrhosis of the liver.

To make matters worse, the immune system sees these adducts as foreign and fires off an inflammatory response. **Around 70 per cent of patients with alcoholic liver disease have anti-acetaldehyde antibodies in their bloodstream.** Drumming up an inflammatory response is usually considered a bad omen as

Some of the best evidence comes from studying people who cannot process the compound normally. **Roughly 50 per cent of people of Japanese, Chinese, Korean or Taiwanese origin carry at least one faulty copy of the ALDH2 gene and can scarcely break down acetaldehyde at all.** The mutation is dominant so even having one copy causes problems.

Flushed faces

The immediate consequences of having the faulty version of the ALDH2 gene are highly visible. “You can see it in any restaurant in Japan or China,” Eriksson says. Almost as soon as these people have an alcoholic drink, **their acetaldehyde levels shoot up to between 6 and 20 times that found in people with normal ALDH2.** This acetaldehyde “rush” triggers **facial flushing, elevated heart rate and dilated blood vessels. Dizziness, headache, nausea and vomiting soon follow.**

Not surprisingly, most flushers tend to avoid alcohol, which is just as well since the long-term health consequences are turning out to be serious. Among the minority of flushers who are also heavy drinkers, the incidence of upper gastrointestinal tract cancer is about 50 times the normal rate. Gene-deficient people also have high rates of head and neck cancer.

There’s more. A recent study of 818 heavy drinkers in Germany found that those individuals who are exposed to more acetaldehyde as a result of a genetic defect – in this case, in the gene for alcohol dehydrogenase – are at greater risk of developing cancers of the upper gastrointestinal tract and liver (*International Journal of Cancer*, vol 118, p 1998). These and a host of other results all add to the growing suspicion that acetaldehyde is a human carcinogen, says Helmut Seitz, professor of alcohol research at the University of Heidelberg in Germany. Mikko Salaspuro, a gastroenterologist at the University Central Hospital of Helsinki, agrees. **“It is likely that acetaldehyde will soon be considered to be carcinogenic in humans,”** he says.

Acetaldehyde also seems to play a role in breast cancer, with up to **5 per cent of all breast cancers attributable to alcohol consumption.** **“The cells don’t forget. This will initiate tumours 20 to 25 years later,”** says Seitz, who is convinced that escalating alcohol intake in the west is linked to rising rates of liver, colon and rectal cancer.

There are even suggestions of a link between acetaldehyde and Alzheimer’s disease. In 2004, researchers at Nippon Medical School in Kawasaki, Japan, reported that among a group of people with Alzheimer’s, the faulty version of ALDH2 was

Acetaldehyde has a fruity taste that is valued in products such as yoghurt



“Only minute amounts of acetaldehyde escape into the bloodstream. But that’s where the problems start”

it takes about 12 hours to eliminate all the ethanol in a bottle of wine. That’s 12 hours of continuous exposure to acetaldehyde, possibly longer. “It remains to be solved how fast acetaldehyde disappears,” says alcohol researcher Peter Eriksson from Finland’s National Public Health Institute in Helsinki.

Irreversible damage

What is becoming increasingly clear is that almost any exposure to acetaldehyde can do serious damage. Acetaldehyde attaches itself to amino groups in proteins to form stable compounds called adducts. According to Onni Niemelä of the University of Tampere in Finland, these cause irreversible damage by **messing up protein structure and function.** In the wake of a drinking bout, a whole range of adducts are formed in the liver, muscles, heart, brain and gastrointestinal tract.

It can result in cell injury and persistent inflammation. **It has been linked with a host of diseases, including rheumatoid arthritis, heart attacks, Alzheimer’s disease and cancer** (*New Scientist*, 22 May 2004, p 40).

Acetaldehyde also attacks DNA. In 2005, researchers at the US National Institute on Alcohol Abuse and Alcoholism in Bethesda, Maryland, reported that acetaldehyde can attack DNA in much the same way it does proteins. The resulting adducts disrupt DNA’s structure and function, and can trigger **mutations and chromosomal problems** (*Nucleic Acids Research*, vol 33 p 3513). These adducts have shown up in the organs of rodents fed alcohol and also in the white blood cells of alcoholics. Little wonder, then, that although ethanol itself is not considered a carcinogen, acetaldehyde is – at least in animals.

There is growing evidence that acetaldehyde is a human carcinogen too.

significantly more common than among a randomly chosen group of healthy people of the same age (*Annals of the New York Academy of Sciences*, vol 1011, p 36).

So who is at risk? As a general rule, most of the excess acetaldehyde you encounter comes from alcohol, and the more alcohol you drink the more acetaldehyde you are exposed to. There is no absolutely safe level of consumption. "It is not necessary to drink huge amounts of alcohol – even low amounts of ethanol taken regularly in a sensitive person increases their risk," Seitz points out.

It's also worth bearing in mind that many alcoholic drinks contain acetaldehyde from the word go. Sherry producers, for instance, encourage acetaldehyde production for its fruity aroma. Calvados is particularly rich in acetaldehyde, and regular calvados drinkers have twice the incidence of oesophageal and oral cancer compared with wine drinkers who consume the same amount of alcohol.

It gets worse. If you smoke, or are exposed to other people's smoke, your acetaldehyde load rises further. Burning tobacco creates acetaldehyde that dissolves in saliva, and acetaldehyde in saliva is a big problem. Unlike the liver with its detoxifying enzymes, the mouth's mucous membranes are pretty poor at breaking down acetaldehyde. As a result, the toxic effects persist for longer.

Among smokers, the risk of oral cancer is 7 to 10 times higher than for people who have never smoked. There are, of course, dozens of carcinogens in tobacco smoke, so acetaldehyde may well not be the only culprit. Nevertheless, an individual smoker's cancer risk is strongly associated with acetaldehyde levels in their saliva and some researchers now believe that acetaldehyde may be one of the principal carcinogens in cigarette smoke.

Combine tobacco and alcohol and the danger multiplies. The effect is synergistic, according to Salaspuro. This could explain the 150-fold rise in oral cancers seen in people who are both alcoholics and smokers, compared with those who abstain from both. "I don't know of any other cancers in which the associations are so strong," Salaspuro says.

Diet dilemma

Acetaldehyde in saliva also comes from the bugs that colonise the mouth and digestive tract. Many of these churn out acetaldehyde as part of their normal biochemistry. Others absorb ethanol from alcoholic drinks and turn it into acetaldehyde. Some people harbour organisms that are particularly good at producing acetaldehyde. "It depends on the kinds of flora you have. There may be huge variations between individuals," says Salaspuro. One mouth-dwelling bug,

Streptococcus salivarius, is particularly good at tossing out acetaldehyde. Another, *Neisseria*, produces 100 times more acetaldehyde when exposed to ethanol compared with other microorganisms isolated from the mouth.

Microbial acetaldehyde production could also explain why people with poor dental hygiene have an increased risk of mouth cancer. The Finnish researchers collected saliva samples from 132 volunteers who differed not only in their drinking and smoking habits but also in the standard of their dental hygiene. The results show that poor dental hygiene comes with a twofold increase in acetaldehyde levels (*Oral Oncology*, vol 37 p 153).

Then there is acetaldehyde in the diet. For centuries, peoples have used bacterial fermentation to produce food – everything from pickles and yogurts to bread and cheese. Where there is fermentation there is

"It gets worse. If you smoke, or are exposed to other people's smoke, your acetaldehyde load rises further"

Freshly brewed coffee is another source of acetaldehyde exposure



acetaldehyde. Acetaldehyde also occurs naturally in ripe fruit and coffee.

"Companies making dairy products sometimes try to increase the acetaldehyde level to give it a special aromatic taste," says Salaspuro. "Some yoghurt producers are searching for new bacteria that are even better acetaldehyde producers." And if you live in a city, there's more. Acetaldehyde is spewed out by vehicle engines. Air pollution adds to the toxic load, though nobody is quite sure how much this affects our health.

With acetaldehyde – and evidence of its toxicity – coming at us from all sides, it's not surprising that scientists are busy developing ways to neutralise the threat. Salaspuro and colleagues at the University of Helsinki, for example, are developing a chewing gum that mops up acetaldehyde. The gum contains a harmless amino acid, L-cysteine, which reacts with acetaldehyde and removes it from saliva.

Last year the team released a study showing that a piece of gum containing just 5 milligrams of L-cysteine could totally eliminate acetaldehyde from saliva if chewed while smoking (*Cancer Epidemiology, Biomarkers & Prevention*, vol 15, p 146). Salaspuro hopes the gum could help prevent digestive tract cancers in those who are most at risk. The gum is being commercialised by a Finnish company called Biohit.

Germ-busting mouthwash could also help. Mouthwash containing the antiseptic chlorhexidine has been shown to slash the numbers of acetaldehyde-producing microorganisms in the mouth, and in a study with 10 volunteers, the Finnish researchers found that treatment with chlorhexidine for three days cut acetaldehyde levels in drinkers' saliva by 40 per cent.

Another solution proposed by the Finnish team is to tinker with the bugs living in your

intestines using prebiotics or probiotics. Lactulose – a harmless, indigestible sugar – is one candidate for the job, says Salaspuro. In experiments with rats, lactulose appears to inhibit acetaldehyde production by making the colon more acidic. Alternatively, ingesting a dose of living microorganisms that don't produce acetaldehyde, such as some *Lactobacillus* and *Bifidobacterium* species, could also help, say Seitz and Salaspuro.

None of these interventions has been shown to prevent cancer, so cannot as yet be recommended as a substitute for a healthy lifestyle. There is still only one sure route to an acetaldehyde-free life: keep it clean. Scrub your teeth, avoid smoke, and next time you're recovering from a hangover, remember to promise your internal organs that this time really will be the last. ●

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