Flavourings to avoid inhaling

Certain flavourings used in cereal product manufacturing processes to give a "buttery" and "creamy" taste can cause severe respiratory illness in workers inhaling them over the long term. Preventive measures and respiratory monitoring of exposed employees are recommended, and the French companies potentially concerned – along with their occupational health services – are asked to exercise vigilance.

The signal

In recent years in France, an occupational disease consultation centre (CCPP) and an occupational health service (SST) have been working together to investigate clustered cases of bronchiolar-type respiratory disorders occurring in a food processing plant making sweet cereal products. This signal was forwarded to the National Network for the Monitoring and Prevention of Occupational Diseases (RNV3P), coordinated by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES).

What we know already

In the United States, clustered cases of severe bronchiolitis obliterans, resulting in progressive irreversible respiratory failure, have been attributed to food professionals inhaling flavourings with a buttery, creamy taste and aroma, which were initially thought to be harmless. In particular, eight cases were described among the 130 employees of a single popcorn manufacturing company, leading to the first real investigations in 2002 [1]. Four of the patients in these cases had severe forms and were awaiting lung transplants.

Due to the context in which they occurred, these occupational conditions were initially described as "popcorn workers' lung disease" (or simply "popcorn lung") and then more correctly as "flavouring-induced lung disease", given the wide range of circumstances in which people can be exposed to these flavourings.

The alpha-diketone- or alpha-dicarbonyl-based flavourings incriminated, are mainly diacetyl (or 2,3-butanedione) but also 2,3-pentanedione, initially used as a substitute for diacetyl, but ultimately found to have similar toxicity.

These substances' mechanism of action on the bronchioles is now well understood. In 2016, the US National Institute of Occupational Safety & Health (NIOSH) published a major reference document on the topic, providing an exhaustive overview of knowledge on hazards, exposures and risks, and setting occupational exposure limits (OELs) [2].

Since then, new publications have regularly corroborated the toxicity of these flavourings [3], and similar occupational cases have been described in the Netherlands and England, as well as a few domestic cases in individuals consuming microwave popcorn on a daily basis [4]. It then became apparent that these flavourings could be found in other occupational contexts, for example in the manufacture of dry biscuits, cereals, chocolate and coffee, and could even be generated by certain industrial processes such as coffee roasting [5, 7]. New cases have been described in these occupational contexts [6].

Investigation and management

When the signal was presented to the Working Group on Emerging Risks, no serious cases of bronchiolitis obliterans related to these flavourings had been reported in France. However, the cases involved raise the issue of the effect that these flavourings may have at much lower concentrations than those found in the index cases published in the United States.

As part of the investigation into these clustered cases, a retrospective longitudinal follow-up of 200 employees from the plants concerned and their pulmonary function tests (PFTs) was carried out, including information on tobacco consumption.

Concerning the occupational factors associated with the results of the PFTs, working in a sector exposed only to raw materials (cereals, flours, and their biological contaminants) was associated with an excess of obstructive ventilatory disorders of the large bronchi, as is typically observed with this type of exposure. However, working in the processed products manufacturing sector was associated with an excess risk of bronchiolar damage, as seen with the flavourings mentioned above. In both cases, tobacco consumption was taken into account. In view of the knowledge of this potential risk from the flavourings, the composition of the ingredients used in the recipe for the products manufactured in these plants was analysed and measurements were taken from the air inside the plants. The latter revealed the presence of diacetyl, which was not mentioned in the product safety data sheets (SDSs) detailing all the substances present in a product and their hazards, and 2,3-pentanedione, which was reported in only one SDS.

The concentrations measured when the products came out of the oven were sometimes higher than those stipulated in the regulations: respectively 3% and 15% of the European (2017) and French[1] (October 2019) OELs.

These flavourings were also detected in the control room, but at lower concentrations, resulting in less intense but longer-lasting operator exposure. This seems to corroborate the results of a cross-sectional study, published in 2014, of 367 employees in a flavouring manufacturing plant that had replaced diacetyl by 2,3-pentanedione [8].

Results showed a doubling of respiratory symptoms and decreased respiratory function in participants who spent at least one hour per day in production areas where the exposure level was twice as high as the US reference values.

Following these results, preventive measures were taken concerning ventilation and employee protection during work on the production line.

Lessons to be learned from this signal

Aside from the severe clinical pictures for high exposures found in the literature, the long-term effects of prolonged inhalation of these flavourings at low concentrations are not yet fully known.

The situation reported here illustrates several key elements in the detection and investigation of new occupational diseases. Firstly, it shows that in the context of a very progressive disease, the link with work is often ignored because there is no improvement to patient complaints during weekly rest days or even holidays (unlike allergic diseases for example). It is therefore necessary to rely on a collective analysis of respiratory function parameters to detect any deterioration in them among certain subgroups of workers. It is then essential to correlate these results with measurements made at the various work stations: concentrations of potentially incriminating substances in the air and in the components handled, even if they are not mentioned in the SDSs. This situation also illustrates the importance of monitoring emerging toxic risks described at the international level, in order to be able to identify them within companies.

When investigating this type of situation, the cooperation of SSTs and CCPPs adds real value; in this case relating to all three of the points mentioned above.

Lastly, it should be remembered that when clusters of identical diseases are observed, occupational physicians, employers, staff representatives or employees may refer the matter to the Occupational Health Alert Groups (GASTs), managed by *Santé Publique France*, which will also seek the expertise of the CCPP(s) in the region concerned.

Moreover, a high-severity signal due to occupational exposure (in this case, from a high-temperature flavouring processing method) raises questions about whether there are any similar situations in other uses. For example, tobacco products and e-liquids designed for vaping often contain flavourings, and are heated during consumption. In recent years, this topic has been addressed in several publications. Researchers have found that a compound in the e-liquids that is chemically similar to diacetyl (2,3-butanolone or acetoin) degrades to diacetyl within the cartridge, whose contents are then inhaled [5,6].

Is it safe to use such ingredients in these tobacco and vaping products? Diacetyl is not currently included in the list of ingredients prohibited in e-liquids. It is the responsibility of the companies marketing the products to ensure that the ingredients they use do not pose a risk to human health. As part of its roadmap on substances of interest, ANSES will examine how to take into account this feedback from a context outside that of tobacco products and vaping.

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1. In France, the regulations stipulate taking 10% of the OEL as a reference value that can be used to consider that the OEL has been complied with. This approach enables the variability of occupational exposure to be taken into account, in particular on the basis of a small number of measurements. https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000021487566.

References

[1] Kreiss K. Recognizing occupational effects of diacetyl: What can we learn from this history? Toxicology. 2017 Aug 1;388:48-54.

[2] NIOSH. Criteria for a Recommended Standard: Occupational Exposure to Diacetyl and 2,3-Pentanedione. 2016 https://www.cdc.gov/niosh/docs/2016-111/

[3] Brass DM, Palmer SM. Models of toxicity of diacetyl and alternative diones. Toxicology. 2017 Aug 1;388:15-20. Hubbs AF. Flavorings-Related Lung Disease: A Brief Review and New Mechanistic Data. Toxicol Pathol. 2019 Dec;4 (8):1012-1026. doi: 10.1177/0192623319879906. Epub 2019 Oct 23.Egilman DS, Schilling JH. Bronchiolitis obliterans and consumer exposure to butter-flavored microwave popcorn: a case series. Int J Occup Environ Health. 2012 Jan-Mar;18(1):29-42

[4] Holden VK1, Hines SE. Update on flavoring-induced lung disease. Curr Opin Pulm Med. 2016 Mar;22(2):158-64. US Centers for Disease Control and Prevention (CDC). Obliterative bronchiolitis in workers in a coffee-processing facility - Texas, 2008-2012. MMWR Morb Mortal Wkly Rep. 2013 Apr 26;62(16):305-7.

[5] Poisson L et al. Generation of α-Diketones and 4-Hydroxy-2,5-dimethyl-3(2H)-furanone upon Coffee Roasting-Impact of Roast Degree on Reaction Pathways. J Agric Food Chem. 2019 Dec 18;67(50):13829-13839.

[6] Vas CA et al. Acetoin is a precursor to diacetyl in e-cigarette liquids, Food Chem Toxicol. 2019 Nov;133:110727.

[7] Cummings KJ et al. Respiratory symptoms and lung function abnormalities related to work at a flavouring manufacturing facility. Occup Environ Med. 2014 Aug;71(8):549 -54.

[8] Cummings KJ et al. Respiratory symptoms and lung function abnormalities related to work at a flavouring manufacturing facility. Occup Environ Med. 2014 Aug;71(8):549 -54.

To find out more, visit:

Occupational Health Alert Groups: https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-liees-au-travail/alertes-en-sante-travail-le-dispositif-gast

Occupational exposure limit values (OELs) for diacetyl

- France: Ministerial Order of 27/09/2019 setting indicative occupational exposure limits for certain chemical agents. The 8-hour OEL for diacetyl is set at 0.07 mg/m3 (0.02 ppm); the 15-minute OEL is set at 0.36 m3 (0.1 ppm)
- Europe: EU Directive 2017/164, the 8h OEL is set at 0.02 ppm or 20 ppb
- US-NIOSH 2016, the 8h OEL (8h TWA) is set at 5 ppb [this NIOSH limit value is based on human data and corresponds to an estimated excess risk of bronchiolitis of 1/1000 in the event of lifetime exposure to diacetyl (8h/d, 40h/week, for 45 years); Park JOEM 2018.

Occupational exposure limit values (OELs) for 2,3-pentanedione

- The MAK value (Germany) is set at 0.02 ppm, i.e. 20 ppb
- US-NIOSH (2016) a TWA of 5 ppb as for diacetyl was desired, but was increased to 9.3 ppb due to the limit of quantification