



To the Minister of Health, Welfare and Sport

Subject : Advisory letter *The health risks of Bisphenol A analogues*
Our reference : U-7831/EvV/pm/789-Y Publication no. 2014/06E
Enclosure(s) : 1
Date : March 19, 2014

Dear Minister,

The use of Bisphenol A has caused a great deal of worry in recent years, as this substance is suspected of being harmful to reproduction and development, metabolism and the immune system.^{1,2} However, it remains unclear how harmful exposure to Bisphenol A exactly is to human beings, and how far exposure therefore must be reduced. Nonetheless, precautionary steps have been taken to manufacture replacements with less unfavourable properties. The industry has created all kinds of compounds chemically related to Bisphenol A. Some of these Bisphenol A analogues have been authorized for usage where otherwise Bisphenol A would be used. However, the question is whether or not such alternatives entail similar health risks. In this letter, the Health Council of the Netherlands addresses this subject. The letter reflects the views of the Committee on Health and Environment Surveillance. It was evaluated by the Standing Committee on Health and the Environment.

Bisphenol A

Bisphenol A is an important raw material for the synthesis of plastics used in medical devices, food packaging and consumer products such as sunglasses and CDs. Additionally, it is used as an additive, for example in printer paper used in thermal transfer printing. Trace amounts of Bisphenol A may leak from all of these materials, possibly resulting in unintentional human exposure to the substance via food, skin contact and the environment.³ In order to prevent health damage caused by exposure to Bisphenol A, the EU has set a maximum daily intake, and set standards for, among other things, materials and products designed to come into contact with food.⁴ As a precaution, baby bottles may no longer be made of Bisphenol A.⁵

How harmful exposure to Bisphenol A is to human beings, and thus how much exposure should be restricted, is a debated topic in the scientific community.^{1,2} In an advisory report on the risks of prenatal exposure to chemicals published today, a Committee of the Health Council of the



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Netherlands concluded that exposure to Bisphenol A prior to birth may have harmful effects on the development of the nervous system.⁶ The health risks of exposure to Bisphenol A in various domains are currently being considered. The *European Food Safety Authority* is conducting an evaluation of its previous position on exposure to Bisphenol A via food sources. The *Scientific Committee on Emerging and Newly Identified Health Risks* of the EU is drafting an advisory report on Bisphenol A in medical devices. At the request of your predecessor and fellow policy-makers, the National Institute for Public Health and the Environment is drafting a report on Bisphenol A that builds on this work. Considering the in-depth reports that are being prepared, this letter does not address recent findings on Bisphenol A, but focuses on findings relevant to insights into the harmfulness of Bisphenol A analogues.

Bisphenol A replacements

Far less research has been conducted into the harmful properties of Bisphenol A analogues than into those of Bisphenol A (see a recent judgement by the French *Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*⁷). Yet, over the past years findings have been published that give cause to question replacement of Bisphenol A with analogues.

Mechanism of action of Bisphenol A and analogues

Bisphenol A and replacements like Bisphenol S and Bisphenol F appear to be able to bind to receptors for female hormones in the body.⁸⁻¹⁰ These oestrogen and oestrogen-related^a receptors play a key role in sexual development and growth processes of, for instance, the brain. The physiologic role of some oestrogen-related receptors is not (yet) clear. Their particular presence in the foetal brain, however, indicates involvement in the differentiation and maturation of nerve cells and corresponding behavioural developments.

Binding properties and chemical structure of Bisphenol A and analogues

Bisphenol A appears to bind almost as strongly to one of the oestrogen-related receptors as natural oestrogens.^{8,13} Various Bisphenol A analogues have the capacity to bind to this receptor, some of

^a The oestrogen-related receptors are named for how they were discovered: by cloning genetic material that codes to oestrogen receptors.^{11,12} Natural oestrogens do not bind to them.



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them equally strongly. Conditions for binding are the presence of one or two phenol groups and several other structural elements in the Bisphenol molecule.¹⁴

Comparison of the oestrogenic properties of Bisphenol A and analogues

The oestrogenic properties of various analogues with phenol groups have been studied and compared to those of Bisphenol A.¹⁵⁻¹⁸ The oestrogenic properties of the analogues studied varied, from ten times as strong as Bisphenol A to ten times weaker. Changes to the phenol groups were found to be responsible for this effect.

Also, the effects of a small number of substances on male hormone balance have been studied.¹⁹ Although some analogues show these androgenic effects, the effects appear at a much higher concentration than the concentration at which oestrogenic effects are observed.

Finally, two other harmful properties were investigated in a small group of Bisphenol A analogues, namely mutagenicity^a and acute toxicity.¹⁵ Like Bisphenol A, the analogues studied did not show any mutagenic properties. Compared to Bisphenol A, acutely they were equally toxic or up to a factor ten less toxic.

So, changes to the Bisphenol A molecule can change its harmful properties. Some weaken the oestrogenic effects, while others amplify them. In general, the hormone-disrupting effects of analogues are no more than one order of magnitude stronger or weaker than those of Bisphenol A. The limited data available indicate an association between the chemical structure of the substances and their harmful properties. The phenol groups play a key role here. The harmful properties of various alternatives, particularly the hormonal effects, are insufficiently well characterized to properly evaluate the safety of their usage.

Conclusion

Available data on receptor binding and hormonal disruption show that the hormonal effects of Bisphenol A analogues vary significantly, and may well exceed those of Bisphenol A. This suggests that Bisphenol A analogues are not necessarily suitable substitutes for Bisphenol A. A more in-depth judgement requires additional research into their harmfulness and the degree to which usage may lead to exposure, for example by leaking out of food packaging. The outcomes of current risk assessments for Bisphenol A may be included in the assessment. This will allow

^a Capacity to irreversibly change information stored in hereditary material.

Gezondheidsraad

Health Council of the Netherlands



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new insights into the risks of exposure to Bisphenol A to be taken into account. The Dutch government would do well to take the position that replacement of Bisphenol A with analogues is currently inadvisable when formulating policy, and to promote this position within the EU and other international regulatory and policy organisations. In doing so, the government could raise the subject of using alternatives unrelated to Bisphenol A. The Belgian High Health Council recently outlined the possible alternatives, with the note that knowledge on their potential harmfulness is also limited.²⁰

I support the conclusion and recommendation of the Committee.

Bisphenol A and its analogues have a broad range of applications, for which policy responsibility is divided among different ministries. Therefore, I have forwarded a copy of this letter to the Secretaries of State for Infrastructure and the Environment, Economic Affairs and the Minister of Social Affairs and Employment.

Yours sincerely,
(signed)
Professor W.A. van Gool
President



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The Committee

The Health and Environment Surveillance Committee has the task of bringing subjects concerning health and the environment to the attention of the government and Parliament, and of highlighting threats and opportunities. This may be in relation to new issues but may equally concern topics that require attention once again.

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Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.