Report on paracetamol and PCA

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Summary

This report was drafted at the request of the Minister for Healthcare and Sport with the aim of investigating whether paracetamol is safe and ensuring that this is the case. The reason for possible concerns in this regard is an article published in the NRC of 9 July 2020 in which the newspaper, based on its own investigation, reports that paracetamol in the Netherlands can contain PCA, which is a potentially carcinogenic substance. This report is a collaborative effort by the Medicines Evaluation Board (MEB) and the Health and Youth Care Inspectorate (IGJ).

It describes how medicines are produced and how the safety of medicines is evaluated and tested. In the course of the chemical production process of every ingredient of a medicine, very small quantities of other chemical compounds, so-called impurities, can be formed. If the production process of paracetamol starts with chlorobenzene, then PCA (para-chloroaniline or 4-chloroaniline can be formed. Several production routes can be used for making paracetamol, including routes whereby no PCA is formed. However, other impurities can be formed in these routes as well. The ability to choose from several production routes for the same ingredient expands the number of options for the production of medicines, which in turn can be an advantage in terms of the availability of medicines.

As impurities can always be formed, safety limits apply to all production processes with regard to these possible impurities so that the health related risk for patients is as small as possible. Some impurities are potentially carcinogenic. The safety limits for potentially carcinogenic impurities are determined on a global basis. Within that context, it has been agreed that the probability of developing cancer is defined as being negligible if no more than 1 additional person out of 100,000 persons develops cancer as a result of being exposed on a daily basis to the highest permissible dosage of a medicinal product during their entire lifetime. The limit for PCA in paracetamol has been set at a maximum of 34 µg per day upon ingestion of the maximum daily dosage of paracetamol.

For medicines, the limits are determined by the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use). For foods, the EFSA (European Food Safety Authority) advises the European Commission regarding the applicable limits. In this report, the differences between the above safety limits are motivated and explained: the EFSA and the ICH use different calculation methods and they also use different studies in calculating their own limit. The measured quantity of PCA in the batches of paracetamol investigated by the NRC remained below the ICH limit that applies to medicinal products. In addition, the limits set for foods cannot simply be applied to medicines as well - an opinion also shared by the ICH and EFSA.

This report also explains how medicines are evaluated and tested before being allowed into the Dutch market. Medicines may be marketed in the Netherlands only if a marketing authorisation has been granted for that purpose. The MEB evaluates and monitors the effectiveness, risks, and quality of medicines and sets conditions for entry into the market. The IGJ supervises and monitors the preparation, the quality, and the use of medicines. The manufacturer of the medicinal product is responsible for the randomised testing of samples in order to investigate the quality of the product. The IGJ carries out checks to ensure that manufacturers actually implement these tests and, for example, also requests the results of these random samples.

After being granted marketing authorisation, the adverse reactions reported and risks associated with medicinal products are continually monitored by the MEB and the EMA (European Medicines Agency). The medicinal product can also be subjected to an independent post-marketing investigation. Within that context, an investigation is carried out to determine whether the medicinal products being marketed comply with the specifications registered with the application for the

marketing authorisation. This laboratory investigation is carried out at the RIVM (National Institute for Public Health). The RIVM reports to the IGJ concerning the results. The RIVM also participates in the network of Official Medicines Control Laboratories (OMCL), a European network in which randomised samples of medicinal products are taken and investigated. The OMCL takes samples each year of many hundreds of medicinal products authorised in the Netherlands, and investigates to what degree they comply with the quality requirements of the product. If, during the above process, it turns out that something is amiss, the fellow inspectorates warn each other and take action. They may, for example, recall a medicine.

In conclusion, the MEB, the IGJ, and their European fellow authorities attach a great deal of importance to the patient safety of medicinal products. However, the formation of impurities during the production of medicinal products cannot be avoided. By setting strict limits, the health risk is minimised as much as possible and therefore becomes negligible. The strict limits set for PCA in paracetamol have not been exceeded. Paracetamol can therefore be used safely by patients in the Netherlands.

Introduction

This report was drafted at the request of the Minister for Medical Care and Sport in response to a recent investigation by NRC and Zembla, which resulted in several publications in the media (Dohmen, et al., 2020). According to these publications, 4-chloroaniline (also referred to as para-chloroaniline or PCA) was detected in three batches of paracetamol produced by the Chinese manufacturer Anqiu Lu'an. No PCA was detected in a batch of paracetamol from a different Chinese manufacturer (Hebei Jiheng Pharmaceutical).

When chlorobenzene is used as a starting ingredient in certain production processes for paracetamol, PCA may be produced as a so-called impurity. No PCA is produced if a different production route for paracetamol is used which starts with phenol. The manufacturer investigated by NRC, namely Anqiu Lu'an, uses the production process starting with chlorobenzene. Strict limits apply to the maximum concentration of PCA allowed in paracetamol, which ensure that paracetamol can be used safely.

The Minister for Medical Care and Sport requested an investigation to be carried out focusing on why PCA is present in paracetamol, which safety requirements apply to medicines to ensure patient safety, and how the Netherlands compares to other countries in Europe. The Minister also asked for an explanation of the different limits applied by European supervisory bodies and why various production processes exist, some of which lead to the production of PCA and some of which do not.

In this report, the MEB and IGJ explain their working procedure and distribution of responsibilities with regard to the requirements and standards for medicines on the Dutch market. The agreements in place between European member states in this regard are also explained. In addition, the role of the EMA and the EFSA and the reason why they apply different standards are also clarified.

Key points of this report

Section 1 describes how the registration of an active substance manufacturer in a medicine dossier is carried out by the MEB as well as the role played by the IGJ in its enforcement. It also describes the role played by European bodies in that regard.

Section 2 deals with the background of PCA. The topics dealt with include the significance of limits set for impurities and how the differences between the limits set by the EFSA and the ICH/EMA can be explained.

Section 3 discusses the roles and responsibilities of the various parties involved in Europe. A description is also given of what the MEB and the IGJ have done and still plan to do in the area of communication and coordination with other parties, including other authorised bodies within Europe as well as patients and consumers.

1. Production of medicinal products

1.1 Production process and quality controls

A medicinal product contains one or more active substances and excipients. The active substance is often produced by a different manufacturer than the manufacturer that produces the final medicinal product. Accordingly, in this report we refer to an active substance manufacturer and a medicinal product manufacturer.

The active substance manufacturer must comply with the European guidelines for good manufacturing practice for active substances (European Union - Good Manufacturing Practice of EU-GMP). The medicinal product manufacturer must ensure that this process includes an initial audit carried out before the active substance is purchased from the producer and that this audit is repeated periodically. As proof of this, the medicinal product manufacturer submits a so-called QP statement with the authorisation application. QP stands for "qualified person", in other words the person who is responsible for authorising the medicinal products of the medicinal product manufacturer in question. In addition, the agreements made by the active substance manufacturer and the medicinal product manufacturer are set down in a written agreement.

If the medicinal product manufacturer is not based in the EU, a written statement must also be submitted by the national authorities of the country where the manufacturer is based. This statement specifies that this manufacturer produces in accordance with rules that correspond to the European rules, that the company is periodically inspected by these national authorities, and that quality defects are reported to the European authorities. The European authorities monitor this during inspection visits paid to the medicinal product manufacturers.

Active substance manufacturers are also visited by European inspectors. This is always the case for producers of sterile active substances for the European market. For producers of non-sterile active substances, it is done on the basis of a risk assessment. For example, based on quality defects reported to the MEB/EMA or the IGJ, the risk may be assessed at such a high level that a decision is taken to pay a visit. An inspection can also be carried out at the request of the MEB/EMA.

A medicinal product that is produced outside the EU must be imported by a manufacturer from an EU country. These medicinal product importers must have an import licence and are regularly inspected by inspectors from the importing EU country.

Every medicinal product that enters a European market must be tested in an EU country before it may be launched on the market. This is a quality control of the medicinal product, whereby tests are carried out on the identity and concentration of the active substance, the amount of impurities, and other important quality characteristics of the medicinal product. Quality control laboratories that carry out these end product tests are regularly visited by the inspectorate. They are required to have a manufacturer's licence (a mandatory licence for every company that manufactures[1] or imports medicinal products) as well as a GMP certificate. This certificate is a confirmation that the company works on the basis of the applicable EU-GMP quality norms, and it is granted by the inspection authority of the country where the laboratory is based.

After being imported, a medicinal product has to be released by a QP in an EU country (certification of a batch of ready to use medicinal products before it can be marketed). The company that releases

[1] **Manufacturing activities** are defined as the complete or partial process of manufacturing a medicinal product, including the primary and secondary packaging process, quality control, and/or release of the product.

a medicinal product for the European market must have a manufacturer's licence for this activity. These companies are regularly inspected by the inspectorate in the country where they are based.

The medicinal product is then stored and distributed within the EU. The company that stores the medicinal product and distributes it within the EU must have a manufacturer's licence or a wholesale supplier's licence for these activities. These companies are regularly inspected by the authorities in the country where they are based.

The medicinal product is sold to a wholesale supplier or pharmacy. The company that sells medicinal products to a wholesale supplier or a pharmacy must have a manufacturer's licence or a wholesale supplier's license. The company must check whether the parties to which they deliver medicinal products have a wholesale supplier's licence or are authorised to supply medicinal products to the public (pharmacists). Inspectors carry out inspections to determine whether the companies actually carry out these checks.

The medicinal product is delivered to the patient by the pharmacist. The pharmacists are also supervised by the IGJ.

The manufacturer is responsible for the quality and safety of the products. After products are authorised for the market, the IGJ monitors the quality of the products by carrying out independent post marketing testing via random sampling. Within that context, an investigation is carried out to determine whether the medicinal products being marketed comply with the specifications registered with the application for the marketing authorisation. This laboratory investigation takes place at RIVM. The RIVM reports to the IGJ concerning the results. RIVM is also part of the European network of national laboratories (OMCL) in which medicinal products are analysed to determine whether they comply with the product's quality requirements. In 2019, these laboratories analysed over 400 products that had been authorised for the Dutch market. In 2018 and 2019, within the OMCL framework, a few products containing 500 mg and 1000 mg of paracetamol were analysed for compliance with the product specifications listed in the relevant authorisation dossier. These products complied with the applicable requirements. If, during the above process, it turns out that something is not as it should be, the fellow inspectorates warn each other and take action, for example by recalling a medicinal product.

1.2 Authorisation process

Medicinal products may be marketed in the Netherlands only if a marketing authorisation has been granted by the European Commission or by the MEB for that purpose. The MEB evaluates and monitors the effectiveness, risks, and quality of medicines and sets conditions for entry into the market. For some medicinal products, the MEB does this by itself, but in most cases it collaborates with the other medicine authorities in the EU and with the EMA.

A company has to submit a dossier if it wishes to have a medicinal product evaluated. This authorisation dossier, which has to comply with current European requirements in terms of content and classification, consists of 5 modules. This report deals only with the requirements for one of these modules, namely Module 3. This module contains the chemical-pharmaceutical data, in other words all data regarding the composition, preparation, and quality controls of a medicinal product. The assessment of medicinal products takes place on the basis of the data that is provided by the authorisation holder. The MEB itself does not carry out any analyses with regard to the composition or production of medicinal products. The assessment takes place only at the administrative level, as the actual testing is already being done by other organisations, and it is therefore unnecessary to repeat the testing.

Module 3 is divided into 2 parts: one part dealing with the medicinal product as a whole (e.g. by tablet or injection), and another part dealing with the active substance. The information about the medicinal product and the active substance is evaluated by competent authorities such as the MEB. Within that framework, a determination is made whether the medicinal product and the active substance comply with the requirements set down in the authorisation dossier.

A medicinal product can contain one or more active substances. For each active substance, one or more active substance manufacturers can be included in the medicinal product authorisation dossier. The medicinal product manufacturer is allowed to work with all active substance manufacturers listed in the dossier. This can differ depending on the specific batch of the medicinal product in question.

The authorisation dossier contains information about every active substance manufacturer. It contains information about the manufacturer, the starting materials for the production route, the production route (the method used to produce the active substance), other (chemical) substances needed for the production, requirements that the active substance must comply with (the specifications), the methods used for testing the active substance, the material in which the active substance is stored, and data from stability studies to substantiate the shelf life. The manufacturer must also demonstrate that the batches produced comply with the applicable requirements. To do so, the manufacturer must submit the analytical results of at least three batches of the active substance. The information must also contain a discussion of the potential impurities, including a discussion of how the presence of potentially carcinogenic impurities can be controlled. Such substances must remain below internationally agreed limits (also see 2.3 for a further explanation of this).

Information about the active substance can be submitted in the medicinal products authorisation dossier in various ways.

- “Full information”. All necessary information about the active substance is submitted in the authorisation dossier by the authorisation holder. The authorisation holder must then be in possession of all the information about the production of the active substance.
- Via the ASMF (active substance master file) procedure. The ASMF is prepared by the manufacturer of the active substance and is submitted by the active substance manufacturer, independently of the authorisation dossier. The authorisation holder has access to a part of the ASMF; the other part contains confidential commercial information from the active substance manufacturer. As the ASMF is submitted independently of the authorisation dossier, the MEB does have access to all the information from the active substance manufacturer, including confidential commercial information.
- Via the CEP procedure. CEP stands for “Certificate of Suitability to the monographs of the European Pharmacopoeia”. The CEP procedure can be used for existing active ingredients for which a monograph is present in the European Pharmacopoeia. A monograph of the European Pharmacopoeia contains requirements for a specific active substance that have been set down by the EDQM (the European Directorate for the Quality of Medicinal products and healthcare, which is part of the Council of Europe). A CEP is granted after the EDQM have evaluated the dossier of the active substance. It is a confirmation that the quality of an active substance can be adequately controlled based on the monograph of the European Pharmacopoeia and the extra requirements that are sometimes listed in the CEP. Authorisation authorities such as the MEB rely on this assessment of the EDQM and accept the CEP as a substitute for the required information for the active substance. The EDQM ensures that the active substance manufacturers who have or request a CEP also produce in

accordance with the CEP. The EDQM does so by carrying out inspections at these manufacturers. If a manufacturer does not meet the requirements, then a CEP can be suspended or revoked.

In the medicinal products with paracetamol that are available in the Netherlands, paracetamol is used from various active substance manufacturers. All these manufacturers have a CEP that has been evaluated by the EDQM. Various starting materials are used in the CEPs for paracetamol that are registered in Europe, including chlorobenzene.

1.3 Distribution of responsibilities for MEB & IGJ

The Medicines Act describes the legally mandated tasks of the MEB (section 2-17) as well as the IGJ (section 100-116) and specifies the legal obligations of manufacturers of a medicinal product (section 26-38) (Overheid, 2020).

Figure 1 gives an overview of the various bodies that are involved in the chain of authorisation and supervision of medicinal products for humans. This figure also shows the same chain for foods.

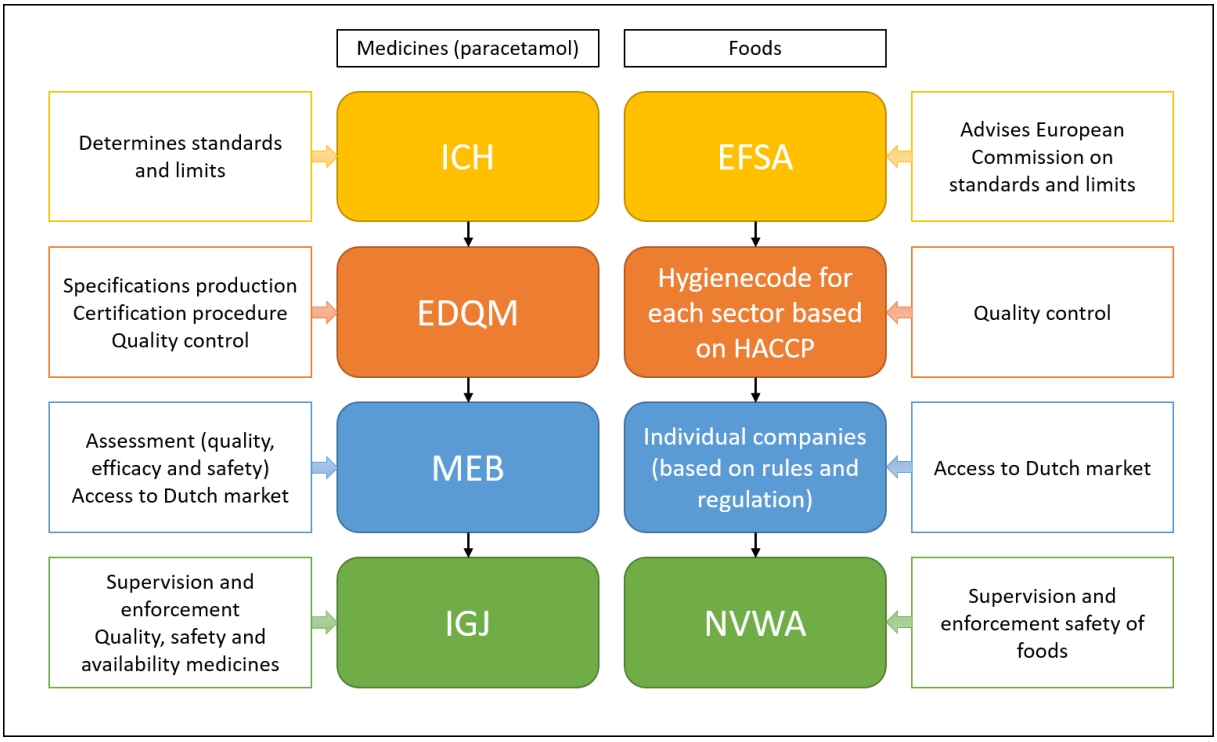

Figure 1 Simplified overview of bodies involved in the authorisation and supervision of medicinal products for humans and foods. The EDQM is involved only in medicines for which a CEP is registered, such as paracetamol. NVWA – Netherlands Food and Consumer Product Safety Authority, HACCP – hazard analysis and critical control points

The European inspection authorities monitor the quality, safety, and availability of medicinal products, whereby the IGJ, on behalf of the Netherlands, monitors companies that have a manufacturer's license and/or wholesale supplier's licence in the Netherlands. This means that, among other things, it performs checks on medicine manufacturers. Whoever markets a medicinal product in the Netherlands is required to report quality defects to the IGJ and the MEB. The MEB and the IGJ collaborate intensively whenever there are problems relating to the quality of medicine. For example, the IGJ decides, based on information from the MEB, whether a market related action (such

as a product recall) should be considered, for example if an active substance is contaminated with an impurity that exceeds the acceptable limit.

Based on the Medicines Act, the IGJ ensures that manufacturers comply with the European guidelines for good manufacturing practice for active substances and medicinal products (EU-GMP). The IGJ also ensures that the medicinal products and active substances produced comply with the requirements set down in the authorisation dossier. If a manufacturer does not produce in accordance with GMP guidelines or if the medicinal products or active substances do not meet the requirements, then the IGJ can implement measures targeting the manufacturers, such as withdrawing the manufacturer's licence or the GMP certificate and/or recalling medicinal products in the Dutch market.

2. Paracetamol production process

Most medicinal products are produced via chemical processes that are often quite complex. In the course of the chemical reactions needed for this, other chemical compounds can also be produced in very small quantities, also referred to as impurities. This is also the case in the production of paracetamol. For example, If the production process starts with chlorobenzene, then PCA (para-chloroaniline or 4-chloroaniline) can be formed. Several production routes can be used for making paracetamol, including routes whereby no PCA can be formed. However, other impurities can be formed in these routes as well.

Safety limits are applied for the potential impurities for all production processes. Some impurities are possibly carcinogenic. The safety limits for potentially carcinogenic impurities are determined on a global basis. Within that context, it has been agreed that the probability of developing cancer is defined as being negligible if no more than 1 additional person out of 100,000 persons develops cancer as a result of being exposed on a daily basis to the highest permissible dosage of a medicinal product during their entire lifetime. For PCA, this limit has been set at a maximum of 34 µg of PCA per day if the person concerned takes the maximum daily dose of a medicinal product.

Manufacturers are obligated to submit a report if a product does not comply with the limits. The inspecting bodies (such as the IGJ) ensure that this actually takes place. No reports have been received in the Netherlands of paracetamol that contains amounts of PCA that exceed the permissible limit. The information published by the NRC also does not indicate that this limit has been exceeded.

2.1 PCA (para-chloroaniline)

Para-chloroaniline (PCA) is potentially carcinogenic (IARC[2] classification 2B). This has been demonstrated in animal studies. However, no studies have been carried out demonstrating that it actually causes cancer in humans.

Most carcinogenic substances damage the genetic material (DNA) present in cells; they are genotoxic without any threshold value, and are therefore referred to as mutagenic. If there is no threshold value, it means that, theoretically, a single molecule of the substance can damage the DNA, in other words cause a mutation. This mutation can then lead to a tumour in the long run. Examples of mutagenic agents include UV light from the sun, x-rays, and certain substances present in cigarette smoke. Not all genotoxic substances are also mutagenic. Some substances can damage DNA via a mechanism that does have a threshold value. As there is no threshold value, a mutagenic genotoxic substance is associated with a greater risk of developing cancer than a non-mutagenic genotoxic substance. The higher the risk level estimated for a substance, the stricter the limit will be for this substance. PCA is a possibly carcinogenic substance, but its carcinogenic mechanism is not 100% certain. That is why PCA is subjected to the strictest limit, as set by the ICH in 2015 (see **section 2.3**).

2.2 Synthesis route

There are various methods available for making paracetamol. They differ in terms of the chemical substance started with and the processing steps that follow. In **Annex 1** you can find a detailed overview of the different production routes used for making paracetamol.

The only one of the various production routes used for making paracetamol in which very small quantities of PCA can be formed is the route starting with chlorobenzene. No PCA is formed on the other routes. However, in the other routes as well, very small quantities of other chemical

[2] IARC – International Agency for Research on Cancer

substances can be formed that can also present risks. This also applies to the routes starting with phenol or nitrobenzene. Phenol and nitrobenzene themselves are also toxic compounds.

It is therefore not possible to identify a safer route for making paracetamol. However, strict safety limits are imposed on all production routes for paracetamol. Banning a specific production route limits the possibilities available for the production of medicinal products, which can in turn have a negative impact on the availability of medicinal products and therefore pose a risk for the patient.

2.3 Limits

The safe limit for a potentially carcinogenic substance in a medicinal product can be determined with the help of guidelines prepared by the ICH. These scientific guidelines are used not only in Europe but also globally (including the US, Canada, Japan, and China). The ICH M7 guideline specifically describes how genotoxic impurities that are formed or can be formed during the production process should be identified, classified, and controlled (ICH, 2018).

In determining limits, a number of assumptions are made in order to arrive at a so-called worst-case scenario, so that the limit is safe for everyone and not only for the average person. This ensures that the limit is still safe even in the most extreme circumstances. These assumptions are as follows: 1) the medicinal product is used on a daily basis, 2) the medicinal product is used throughout one's lifetime, 3) the medicinal product is used in the maximum dosage, and 4) the body weight of an adult patient is 50 kg.

Based on these assumptions (i.e. worst-case scenario), if the limit is reached for mutagenic genotoxic substances without a threshold value, the risk of cancer will lead to 1 additional person developing cancer per 100,000 persons (i.e. negligible). If all of these assumptions do not apply (i.e. if the quantity of the medicinal product ingested is less than the quantity dictated by the first 3 assumptions or if the bodyweight is higher than 50 kg), then the actual risk involved is even less than the negligible risk referred to above. For substances that are genotoxic but do have a threshold value, there will be no risk below the defined limit, and toxicity will only occur above the threshold value.

In **Table 1** you can see which limits are applied by the ICH (ICH, 2018) and by the EFSA (EFSA, 2015). The points of departure used by the ICH and the EFSA are also specified and are further explained in **section 2.5**.

Table 1 *Limits for PCA applied by ICH and EFSA. µg = microgram, ppm = parts per million. TD50 and BMDL10 are calculation methods used by ICH and EFSA; they are explained further in section 2.5.*

	Point of departure	Point of departure for calculation	Extrapolation factor	Limit in µg/kg body weight	Limit for a person weighing 50 kg	Limit in ppm	
						Maximum dosage 3 g/day	Maximum dosage 4 g/day
ICH 2015	Liver tumours in mouse, no threshold value	TD50 = 34 mg/kg	50,000	0.68 µg/kg	34 µg/day	11 ppm	8 ppm
EFSA 2015	Spleen and adrenal gland tumours in rats, no threshold value	BMDL10 = 0.56 mg/kg	10,000	0.056 µg/kg	2.8 µg/day	1 ppm	0.7 ppm

The concentration of PCA found in the batches of paracetamol investigated by the NRC was 5 mg/kg and the concentration of raw material for paracetamol was 6 mg/kg. This is 5 ppm and 6 ppm, which is below the ICH limit but above the EFSA limit. The MEB follows the ICH limit, as this limit applies to medicinal products. Very small quantities of PCA are therefore allowed to be present in paracetamol. As long as the quantity of PCA remains below the ICH limit, the manufacturer does not have to report it to the authorities, and no market actions (such as recall actions) are taken by the MEB and IGJ.

2.4 Controls on PCA during the production of paracetamol

All raw materials for paracetamol used in the production of medicinal products in Europe must, as a minimum, comply with the limits described in the monograph for paracetamol of the European Pharmacopoeia. The monograph for paracetamol does not specify any limit for PCA itself, but the quantity of PCA is indirectly controlled by the limits of 2 other impurities.

This control strategy works as follows (also see **Figure 2**). In the last step of every paracetamol production process, para-aminophenol (K) is converted into paracetamol via a reaction with acetic anhydride. A limit has been set for impurity K in paracetamol to ensure that this conversion is complete. When chlorobenzene is used as a starting material for the production process of paracetamol, PCA can be formed during previous steps. This PCA is converted into chloroacetanilide (J), also with acetic acid, in the same step as is para-aminophenol. A limit of 10 ppm is specified in the paracetamol monograph for impurity J (chloroacetanilide).

The combination of both limits, the limit for impurity K and the 10 ppm limit for impurity J, ensures that the ICH limit for PCA in paracetamol will not be exceeded.

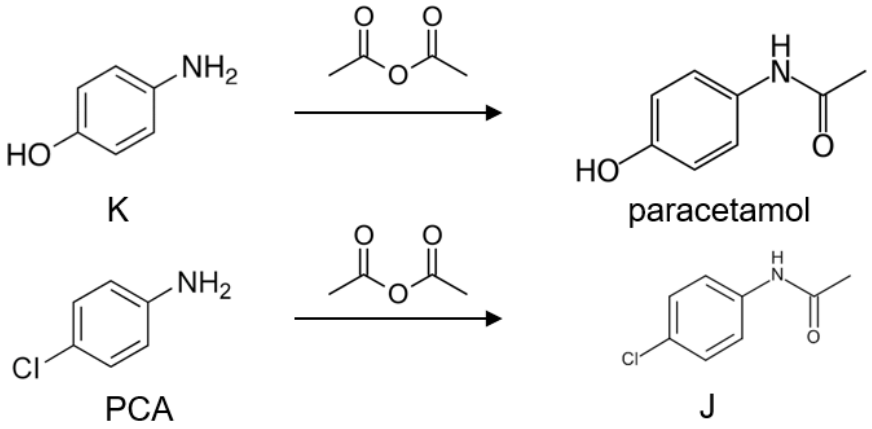

Figure 2 Paracetamol production and impurities

2.5 Difference between EFSA and EMA/ICH limits

Generally speaking, stricter limits are set for foods than for medicinal products, as there is no maximum daily dosage for foods as opposed to medicinal products. Accordingly, it is possible to ingest a much greater quantity of a potentially carcinogenic impurity via food than via medicinal products. Another general point worth mentioning regarding the difference between limits that apply to food and to medicinal products is that, in contrast to foods, a medicinal product is used to treat or prevent a sickness or to reduce symptoms/effects. That is also why higher limits of harmful substances are acceptable in the case of medicinal products. The benefits of medicinal products then outweigh the possible disadvantages. In the case of foods, the assessment is carried out only on the basis of the potential risk involved.

As described in **section 2.3** there is a difference between the limits applied by the EFSA and the ICH, which have been in place since 2015 and were referenced by the NRC. This difference is caused by two factors: 1) the EFSA and the ICH use different calculation methods, and 2) the EFSA and the ICH make use of different studies in calculating the limit. This is briefly explained below; in **Annex 2** a more detailed explanation of the differences is presented.

The EFSA and the ICH use different calculation methods for calculating a limit for mutagenic and genotoxic substances. These methods are based on animal studies and both have their advantages and disadvantages. The BMDL10 method is the standard method used by food toxicologists, and the TD50 method is used by medicinal product toxicologists. In the end, the same risk is calculated by both methods, namely the risk that one additional person out of 100,000 will develop cancer in the case of lifelong daily exposure to the concentration in question. Furthermore, both methods differ in the interpretation of the studies used by the EFSA and the ICH for the calculation.

Several animal studies have been carried out to investigate the carcinogenicity of PCA. The most important of these are a 103-week study in rats and a 103-week study in mice. In the study using rats, tumours developed in the adrenal gland and the spleen, whereas in the study using mice, tumours developed in the liver. The ICH used the mice study for its calculations, whereas the EFSA used the rat study. As the rat study saw tumours developing at lower dosages, the EFSA calculated a lower limit.

2.6 Agreements with regard to impurities during the production process

As mentioned earlier in **paragraph 2.3**, international agreements regarding controls on mutagenic impurities in medicinal products are set down in the ICH M7 guideline. This guideline specifies that the presence of (potentially) mutagenic impurities in a medicinal product must be limited to the level at which the potential risk of people developing cancer due to exposure to these potentially mutagenic impurities is negligible. The appropriateness of these international agreements was recently confirmed during discussions regarding an article 5(3) procedure[3] for nitrosamines.

Nitrosamines are impurities that can be formed in medicinal products, for example during the production process. An example of this is the production process for the "sartans" (losartan, valsartan, etc.). During this article 5(3) procedure, the avoidance principle was discussed, i.e. completely avoiding the formation of impurities, for example by banning certain production routes.

The conclusion of this discussion was that the avoidance principle should not be applied (EMA, 2020). Implementing the limits for acceptable intake, as described in ICH M7, is sufficient to guarantee patient safety. Application of the avoidance principle limits the possibilities available for the production of medicinal products, which can in turn have a negative impact on the availability of medicinal products and therefore pose a risk for the patient.

The current European agreements, set down in ICH M7 and once again discussed in the context of the article 5(3) procedure, with regard to limiting the presence of impurities also apply to (potentially) mutagenic impurities in paracetamol. The limit for PCA, as set down in ICH M7, is sufficient to guarantee patient safety.

[3] Article 5(3) of Regulation 726/2004 mentions the possibility of having a specific procedure started by the director of the EMA or at the request of the European Commission. In this procedure, a scientific topic is discussed that is important for the evaluation of medicinal products and for which an opinion is desired from the CHMP (the decision-making body of the EMA).

3. Past and future actions by MEB/IGJ

MEB

The MEB has had extensive contacts with various European stakeholders. The EFSA was contacted via the EMA in order to obtain greater insight into the difference between the limits applied by the ICH and EFSA. Via contacts with the EDQM, the MEB obtained insight into the various authorised CEPs for paracetamol and into which limits are specified herein for the purpose of controlling PCA impurities. The MEB also informed its fellow authorities in the other EU member countries regarding the situation via the CMDh. The CMDh supports of the approach taken by the MEB.

In response to the commotion caused by the NRC article, the MEB quickly announced that it was already known that PCA can be present in paracetamol and that this is subject to very strict limits, which have not been exceeded. In addition, the MEB published a Q&A with answers to frequently asked questions in collaboration with patients and caregivers (CBG, 2020). The Q&A drafted by the MEB was translated into English and shared with fellow authorities and the EMA, and it forms the basis for a shared communication line within Europe.

The NRC requested information from the MEB on which companies are allowed to market paracetamol on the Dutch market, and which companies are delivering which materials to which parties. Parliamentary questions were also asked on this topic. The MEB receives questions regarding specific medicinal products and manufacturers fairly frequently. Such information is considered to be of a commercially confidential nature. Based on collective agreements, the MEB does not provide this information. The manufacturer itself is responsible for releasing such information. The MEB has worked out the details of this policy in its policy on the implementation of the Freedom of Information Act (Wob). This is explained further in **Annex 3: Public** disclosure of information **disclosure of information**.

IGJ

The IGJ has received information from the company Apotex Nederland BV regarding the active substances used for the production of their products containing paracetamol. Over the period from 1 January 2019 up to and including 7 July 2020, the company processed 144 batches of paracetamol from the two Chinese suppliers of active pharmaceutical ingredients mentioned in the NRC investigation.

Both manufacturers of active pharmaceutical ingredients submitted CEPs which demonstrate that the production route for the ingredient complies with the applicable monograph of the European Pharmacopoeia. These documents refer to the limit for impurity J (chloroacetanilide) and the limit for 4-aminophenol (referred to as impurity K) in the material.

The IGJ also viewed the analysis certificates. The certificates contain the results of various chemical analyses of the batches investigated that are mandatory for the active substance in question. The IGJ compared the results obtained for the two impurities with the limits. In all the analysis certificates received, the two impurities were either not detectable or far below the limit.

No direct measurements of PCA were contained in the analysis certificates received. Via Apotex Nederland BV, the IGJ has received information from active substance manufacturer Anqiu Lu'an showing that the concentration of PCA in 44 batches delivered to Dutch customers in the first half of 2019 was below the detection limit of 0.8 ppm. The EDQM has confirmed the results of these analyses and makes it clear that this has no consequences for the safety of paracetamol (EDQM, 2020).

The concentrations of PCA mentioned in the NRC investigation were below the applicable limit. The additional data seen by the IGJ do not give the IGJ any reason to assume that other paracetamol products contain PCA concentrations that do exceed the applicable limit. The IGJ therefore sees no indication at all of a deviation or product defect entailing risks for patient safety. In the opinion of the IGJ, it is therefore not necessary to take market related actions or carry out any additional research.

Conclusion

By-products or impurities are formed during the production process of every medicinal product. This is unavoidable. Strict limits are set for these impurities in order to limit the potential risks for the patient. When paracetamol is produced via the chlorobenzene route, the impurity PCA can be formed. PCA is subject to a strict limit, which has been determined, accepted, and applied by several international bodies. Neither the data published by NRC nor the additional information reviewed by the IGJ on the basis of the data that it received provides any indication that the limits for PCA in paracetamol have been or are being exceeded.

The MEB, the IGJ and their European fellow authorities attach a great deal of importance to the patient safety of medicinal products. Careful procedures have been developed for evaluating the quality and safety of medicinal products as well as for monitoring these aspects. These procedures ensure that medicinal products marketed in the Netherlands are safe. European agreements and globally applicable limits form the point of departure in this regard. The fact that different European and international bodies set different limits for impurities, including PCA, can cause some confusion. The setting of limits is a dynamic field of endeavour, where differences can occur due to the use of different calculation methods and different points of departure as well as new scientific insights.

The publication in the NRC has caused some unrest. The publication creates the impression that the process of evaluating the safety of medicinal products and authorising and supervising their use is inadequate. This report describes how this process is structured and how patient safety is always the primary point of departure throughout this process. This report makes it clear that there is no contamination of paracetamol and that the limits were not and are not being exceeded. With this report, the MEB and the IGJ wish to confirm once again that the strict limits set for PCA in paracetamol have not been exceeded. Paracetamol can therefore be used safely by patients in the Netherlands.

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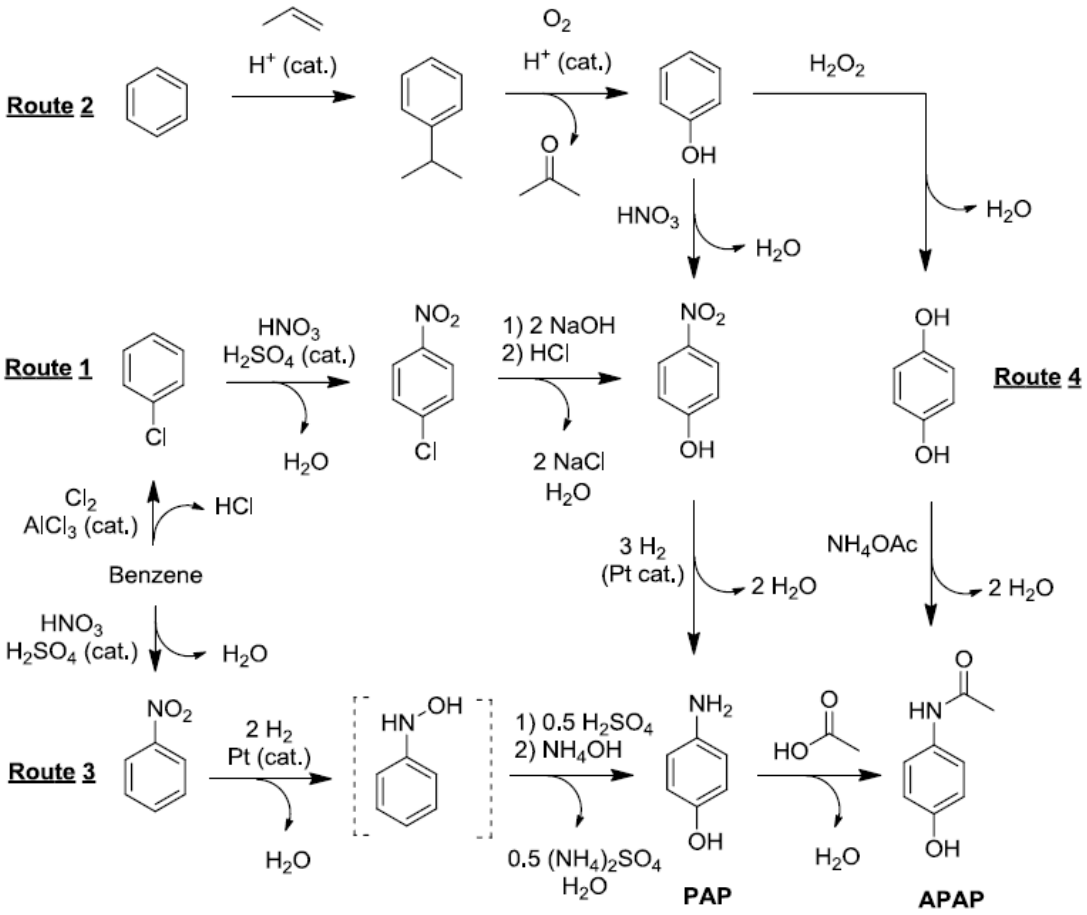
Appendices

Annex 1: Paracetamol production routes



Paracetamol production routes – **route 1 (chlorobenzene):** nitration of chlorobenzene; **route 2 (phenol):** nitration of phenol; **route 3 (nitrobenzene):** reduction of nitrobenzene; **route 4:** amidation of hydroquinone. PAP is the abbreviation of **p**ara-**a**mino**p**henol. APAP is the abbreviation of the official chemical name of paracetamol; **a**cetyl-**p**ara-**a**mino**p**henol. (Joncour, et al., 2014)

Annex 2: Further explanation of the differences between the EMA and EFSA limits

The EFSA and the ICH use different calculation methods for calculating limits for mutagenic genotoxic substances, as was done in 2015. The EFSA uses the BMDL10 method and the ICH uses the TD50 method. Both methods are based on animal studies and both have their advantages and disadvantages. The BMDL10 method is the standard method used by food toxicologists, and the TD50 method is used by medicinal product toxicologists.

The BMDL10 method uses a calculation model that is based on a dose-response relationship in order to predict a dosage that would result in an incidence of 10% of tumours in animals (the BMDL10). A safety margin of 10,000 is then applied to this calculation. This method does not calculate any quantitative value (for example a risk factor of 1 out of 100,000), but instead talks of "low concern" if the value remains below the limit. In numbers: the BMDL10 of PCA according to the EFSA is 0.56 mg/kg, which after being divided by 10,000 is 0.056 microgram/kg = 2.8 microgram PCA for a person weighing 50 kg.

The TD50 method uses the dosage at which 50% of the animals develop tumours as the point of departure. Then, via linear extrapolation and an extrapolation factor of 50,000, an incidence of 1 out of 100,000 is calculated. This works out to 34 micrograms of PCA for a person weighing 50 kg.

Even though the BMDL10 method does not provide any quantitative values, if you compare the numbers, both calculations end up providing the same results. After all, 10% divided by 10,000 is also 1 out of 100,000. In principle, both methods should therefore calculate comparable values (same order of magnitude). The methods also differ in terms of the studies used by the EFSA and the ICH for the calculation.

The EFSA as well as the ICH set a limit for PCA, as they have assumed since 2015 that PCA is potentially mutagenic and genotoxic (reacts with DNA), without any threshold value, and therefore carcinogenic. Information about this potential genotoxicity can be derived from in vitro testing and from long-term carcinogenicity studies in rats and mice. Several animal studies have been carried out to investigate the carcinogenicity of PCA. The most important of these are a 103-week study in rats and a 103-week study in mice. In the study using rats, tumours developed in the adrenal gland and the spleen, whereas in the study using mice, tumours developed in the liver.

The ICH has interpreted the results of the rat studies and finds that the mechanism behind the development of these tumours cannot be based on genotoxicity but on a completely different mechanism that does have a threshold value. In such a case, linear extrapolation to a risk of 1 out of 100,000 does not take place, as such an extrapolation only applies to mutagenic genotoxic substances. A different approach is then used here, which is based on a NOAEL (no observed adverse effect level, i.e. the dosage at which no tumours develop), and where several safety factors are used to calculate an acceptable daily intake (ADI). This will then be higher than a limit for mutagenic genotoxic compounds. The rat study was therefore not included by the ICH in the calculation of the ADI for PCA.

For the liver tumours in the mice study it is not certain, according to the ICH, whether a genotoxic mechanism is actually involved (and therefore whether PCA is in fact genotoxic), but this can also not be excluded with any degree of certainty. It was therefore assumed that a mutagenic genotoxic mechanism was involved, and the limit set by the ICH is based on this study of liver tumours in mice. The TD50, i.e. the dosage at which 50% of the animals develop a tumour, was 34 mg/kg. Using an extrapolation factor of 50,000, this leads to an ADI of 34 micrograms per day for a person weighing 50 kg.

In 2015, the EFSA interpreted the results of these two studies differently and is of the opinion that a mutagenic genotoxic mechanism cannot be excluded for the adrenal gland and spleen tumours in the rat studies. The EFSA BMDL10 calculation is therefore based on the rat studies, where tumours already developed at a lower dosage, thereby leading to a lower limit .

Other evaluating bodies interpret the results of the rat study and the mice study in the same way that the ICH does.

- The ECHA (European Chemicals Agency) declares that: “PCA is positive in some in-vitro genotoxicity assays but there is no evidence of a primary genotoxic activity in vivo.” They therefore go a step further than the ICH and conclude that PCA is definitely not genotoxic in vivo (ECHA, 2020). The ECHA does not specify a limit for the maximum acceptable daily intake.
- The WHO (World Health Organisation) concludes: “Whether the mechanism of carcinogenesis is mediated through genotoxic or non-genotoxic events is unresolved. PCA is genotoxic in vitro but appears to be dependent on metabolism for its full expression.” The WHO then calculates a limit based on a non-genotoxic mechanism (WHO, 2003). So the WHO also goes further than the ICH in this matter and is less strict. The limit calculated by the WHO is 2 microgram/kg, which is 100 microgram for a person weighing 50 kg.

In 2018, the EFSA worked on a review with regard to the toxicity and associated limits for PCA (EFSA, 2018). The review took place within the framework of a renewal (reauthorisation) for the pesticide diflubenzuron. PCA is a metabolite of diflubenzuron. The EFSA limit dating from 2015 was determined on the basis of the information then available on diflubenzuron and PCA. In this review, new studies by the manufacturer were reviewed and discussed within various scientific organs of the EFSA. This discussion focused primarily on the manner in which PCA is genotoxic. In the draft report of the review, the proposed limit for PCA is many times higher than the EFSA limit from 2015. However, this review was never completed, as the manufacturer withdrew the reauthorisation request for diflubenzuron. The EFSA limit from 2015 is therefore no longer updated on the basis of new scientific insights.

Annex 3: Public disclosure of information

Based on collective European agreements, the MEB does not provide any confidential commercial information. The manufacturer itself is responsible for releasing or not releasing such information. The MEB has worked out the details of this policy in its WOB (Freedom of information) policy.

Wob and exceptions

Matters that involve public access to information are dealt with on the basis of national legislation. The MEB therefore bases itself, in matters involving public access to information, on the Freedom of Information Act (Wob). The point of departure of the Freedom of Information Act (Wob) is that all documents which the MEB has in its possession and which relate to a governmental matter which concerns the MEB, are public. Information can only be kept confidential insofar as it is covered by one of the grounds for exceptions referred to in Articles 10 and 11 of the Wob.

EMA/HMA guideline regarding public disclosure of confidential commercial information

In evaluating whether grounds for an exception apply, the MEB also uses a guideline (EMA, 2012) whose content has been agreed upon by the European Medicines Agency (EMA) and the European collaborative body of national competent authorities (HMA). This guideline specifies that information on the manufacturer/manufacturers of the active substance/substances and the place/places where the substances are manufactured is of a confidential commercial nature. This means that, as a rule, this information cannot be released. In October 2019, most of the member states (including the Netherlands), in a meeting of the Coordination Group on Mutual Recognition and Decentralised Procedures for human medicinal products (CMDh), supported this guideline (CMDh, 2019). In applying this guideline, 'confidential commercial information' is defined as: all information that is not available in the public domain or via public sources and the public disclosure of which could undermine the economic interest or competitive position of the owner of the information.

Working out the details of the guideline at the national level

In the MEB working document in which basic agreements on the content of the grounds for exception have been worked out, (CBG, 2019) it was agreed, based on the European guideline, that within the framework of article 10, paragraph 1, introduction and under c of the Wob, the names of manufacturers or suppliers of active substances, excipients, and solvents would not be released, as this is considered to be confidential company and manufacturing information.

Until now, within the implementation framework described above, the MEB has not publicly disclosed any information about manufacturers of active pharmaceutical ingredients if the information is related to a specific medicinal product. However, the MEB does disclose the name of the manufacturer involved in the release. This is the manufacturer responsible for releasing a batch of the medicinal product. Information regarding this manufacturer is printed on the package leaflet of the medicinal product and can be consulted in the MEB Medicines Information Bank. In case of a safety issue, this makes it possible to quickly take measures should this become necessary from the perspective of public health protection. This working procedure has also been coordinated within a European framework.

The fact that a different member state (such as Italy) does disclose the name of an active substance manufacturer within the context of the national situation is a consequence of the policy freedom enjoyed by member states within the EU with regard to public disclosure of information. As a result, member states can implement differing policies with regard to the same issues.