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Endocrine-disrupting pharmaceuticals in the environment

How Aspen API is acting to minimize discharges of hormone-based active pharmaceutical ingredients into the environment.

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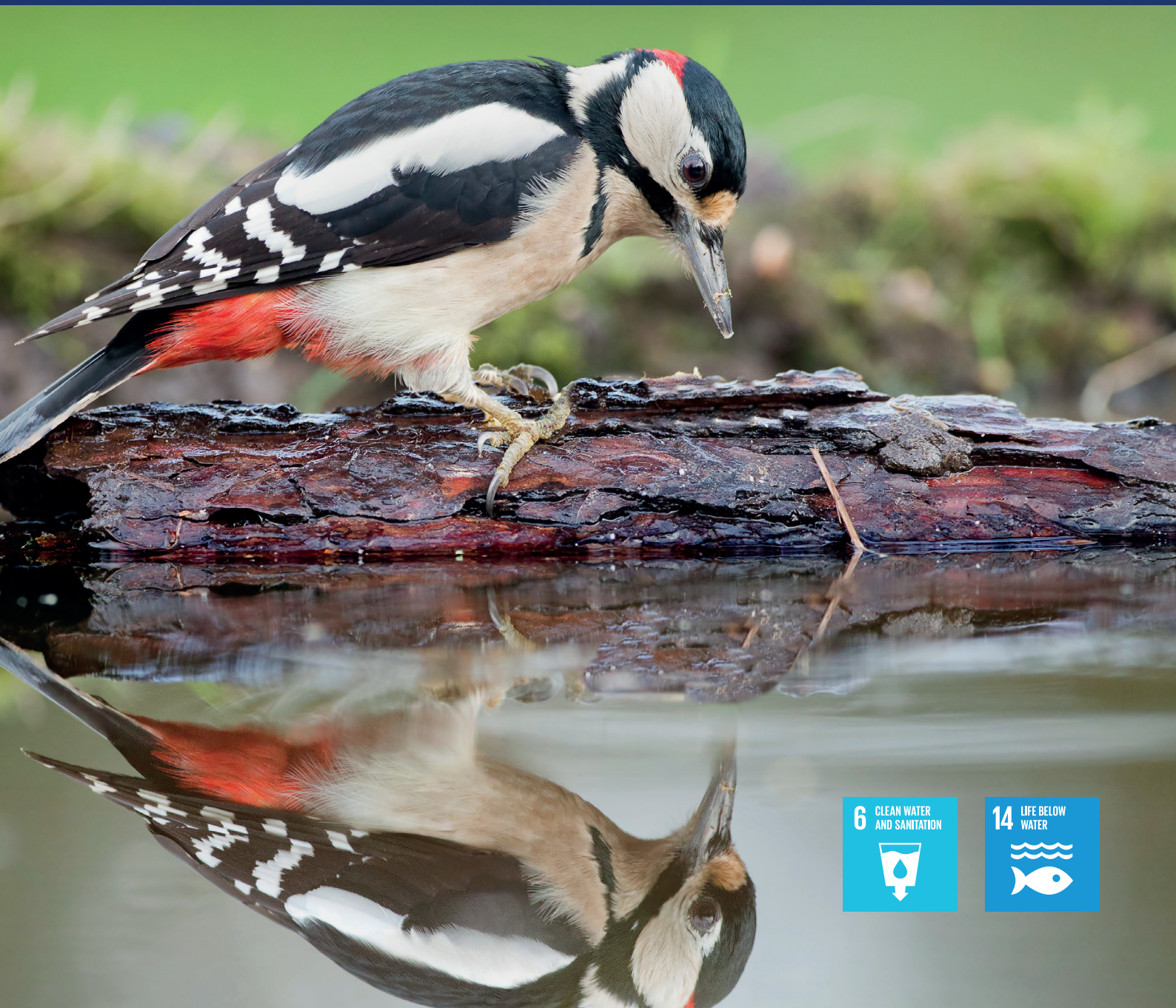


Summary

"In our effort to preserve this world for generations to come, we try to minimize our footprint. In this paper, we explain how we operate our manufacturing plants in the Netherlands, with a view to eliminating API discharges to the environment."

Jos Dingemans
Manager Environment

98% **reduction**

Aspen API has successfully reduced API discharges by 98% in recent years.

Executive summary

Active pharmaceutical ingredients (APIs) are recognized as a contaminant of emerging concern for environmental and human health. Designed to be biologically active, APIs are also developed *to remain stable during their passage through the body. However, due to their persistence, they can accumulate in the environment with potentially significant impacts on both the environment and non-target organisms. In total, more than 770 pharmaceuticals and their metabolites can be found in the environment. Even in low concentrations, the risks associated with pharmaceuticals in the environment (PIE) need to be determined and carefully managed, with a view to minimizing their impact on people and the environment.*

A growing source of API emissions is estrogenic hormones such as oral contraceptives and hormone replacement therapies, known within the chemical industry as endocrine-disrupting chemicals (EDCs). As a leading producer of estrogenic hormone APIs, Aspen API is committed to minimizing the health and environmental impact of our manufacturing activities. This white paper outlines efforts to tackle this growing health issue, including the steps we are taking in our manufacturing facilities in the Netherlands to fully eliminate our API discharges into the environment.

EDC emissions: An underreported concern

As patient demand for, and subsequent production of, natural and synthetic hormones increases, EDC discharges have become a growing health and environmental issue around the world, and particularly in major producing regions such as Europe. However, industry awareness around the health and environmental impact of EDC emissions can be considered underdeveloped compared with other areas of pharmaceutical production.

Pharmaceutical residues enter the environment at all stages of their lifecycle. They can re-enter terrestrial systems and spread to surface waters and agricultural lands. Medicines also enter the environment through human excretion via wastewater and animal excretion via runoff from agricultural areas and discharges from aquaculture. Reportedly, between 30% and 90% of oral doses are generally excreted as active substances[1]. A further key route is through improper disposal, including unused medicines being disposed of via toilets or sinks. Current wastewater treatment plants are unable to entirely destroy or remove pharmaceuticals, and residues are known to accumulate in fish, vegetables and livestock. They can also appear in drinking water.

The issue of PIE is gaining attention from outside the scientific community, with increased scrutiny from media, governments, regulatory agencies, and investors. These concerns are also recognized by the United Nations Environment Programme, as well as by the World Health Organization (WHO) within its Strategic Approach to International Chemicals Management, where EDC and Environmentally Persistent Pharmaceutical Pollutants (EPPPs) have been highlighted as an emerging policy issue[2].

Low concentrations of pharmaceuticals in the environment are known to adversely affect animals and other organisms. This raises questions about how humans may be affected by continuous, long-term exposure. There are three groups of pharmaceuticals that are particularly active in low concentrations and have therefore attracted the attention of researchers, policymakers and environmental experts: antibiotics, anti-cancer treatment drugs, and steroid hormones[3].

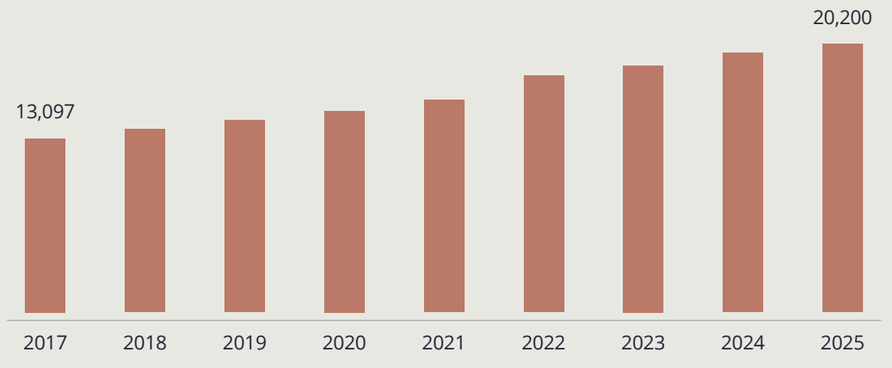
[1] Executive Agency for Health and Consumers – Study on the environmental risks of medicinal products – December 2013
[2] UN Environment Programme – An Assessment Report on Issues of Concern: Chemicals and Waste Issues Posing Risks to Human Health and the Environment – September 2020
[3] Christian G. Daughton, Pharmaceuticals and the Environment (PiE): Evolution and impact of the published literature revealed by bibliometric analysis,Science of The Total Environment, Volume 562, 2016, Pages 391-426, ISSN 0048-9697, https://ec.europa.eu/info/sites/default/files/study_report_public_consultation_pharmaceuticals_environment.pdf https://www.who.int/water_sanitation_health/publications/2011/pharmaceuticals_20110601.pdf
[4] World Health Organization – No time to wait: Securing the future from drug-resistant infections – April 2019
[5] Environmental Science and Pollution Research - Fate and effects of the residues of anticancer drugs in the environment – June 2016
[6] International Journal of Molecular Science - Current Knowledge on Endocrine Disrupting Chemicals (EDCs) from Animal Biology to Humans, from Pregnancy to Adulthood: Highlights from a National Italian Meeting – June 2018
[7] Fortune Business Insights – Contraceptive Pills Market to Reach USD 20.55 Billion with 5.8% CAGR by 2026 – December 2019

The growth of drug-resistant bacteria due to antibiotic misuse has become increasingly well-publicized. This is in part due to the increasing visibility of drug-resistant infections, which contribute to an estimated 700,000 patient deaths each year[4]. Similarly, the rapid development of cancer treatment drugs as a therapy area has brought oncology pharmacology increasingly into the spotlight, with cancer therapies known to have mutagenic, carcinogenic, and teratogenic properties, and potentially also damaging reproductive systems[5].

Awareness of EDC emissions trails demand
Compared with other API product groups, the effects of endocrine (or hormone) disrupting pharmaceuticals are relatively unexplored within the healthcare industry. However, the impact of such products is no less harmful: medicinal hormones such as estrogen-containing oral contraceptives are known to accumulate in drinking water and other aquatic environments at concentration levels that present a significant risk to animals and wildlife. Exposure to even very low doses of endocrine-disrupting compounds can cause harm to humans, as any change to the body's sensitive endocrine functioning can cause significant developmental and biological effects. Studies have linked exposure to endocrine-disrupting chemicals (EDCs) to multiple health conditions, including infertility, early onset puberty, developmental malformations, increased cancer risk, and disturbances to the immune and nervous systems, among various other issues[6].

Growing patient demand for common oral contraceptives, in particular, suggests the health and environmental impact of EDC emissions is set to intensify in the coming years. According to Fortune Business Insights, the global market for oral contraceptives is projected to exhibit a compound annual growth rate (CAGR) of about 6%, with worldwide sales on track to exceed USD 20 billion by 2025[7] (see Figure 1).

Figure 1: Global contraceptive medication market size 2017-2025 (USD million)



Source: Fortune Business Insights

As in the case of other APIs, estrogenic contraceptives and other hormone-based medications are not easily biodegradable, which makes safe waste treatment methods essential during the manufacturing phase. With production growing year-on-year, the pharmaceutical industry has a responsibility to establish and maintain best practice in the production and safe disposal of potentially harmful APIs. Health Care Without Harm (HCWH) Europe, an international nongovernmental organization (NGO) that is financially supported by the European Commission's (EC) LIFE Programme, advocates a multi-sectoral, multi-stakeholder approach to minimize and prevent the API discharges throughout the different lifecycle stages of production, use and disposal[8].

Within this approach, the HCWH sets out a series of recommendations and actions for pharmaceutical producers to minimize the discharge of APIs to the environment during production.

The HCWH promotes the Extended Producer Responsibility concept, through which pharmaceutical manufacturers would be required to finance collection schemes under the extended producer responsibility clause of the Waste Framework Directive. The HCWF also emphasizes the need for Pharmaceutical companies to have clear oversight of their supply chains to ensure consistently high standards throughout the product lifecycle, and to report publicly on their environmental and worker safety standards.

[8] HCWH - HCWH Europe Recommendations on pharmaceuticals in the environment - September 2016

Our solution to eliminate EDC emissions

As a producer of active pharmaceutical ingredients including estrogenic hormones, at Aspen API we recognize our responsibility to limit the impact of pharmaceutical waste streams at this important stage of the production lifecycle. We maintain close control over our API manufacturing processes and the wider lifecycle impact of our products, and we ultimately aim to reduce our wastewater and airborne API emission to zero. As part of this ambition, we have taken steps to significantly strengthen our disposal processes for EDCs.

Aspen API's production of natural and synthetically produced hormones takes place primarily at our three facilities in the Netherlands: De Geer, Moleneind and Boxtel (see below). These manufacturing sites are equipped with a process that secures our goal to achieve zero API discharge and treats all APIs equally. The efficacy of the API removal process is monitored by observing the four APIs known to have adverse effects, which are representative of all APIs produced by Aspen API.

Environmental risk assessments (ERAs) are undertaken at Aspen API's production facilities in the Netherlands, forming a central part of our validation process for new product development. We closely evaluate our compliance with Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation, as well as with standards for chemical safety, waste stream management and environmental emissions before introducing new production processes into the site. After this, we continue to strictly

Our Dutch manufacturing sites

De Geer

Oss, The Netherlands

The De Geer ('Diosite') facility is dedicated to chemical manufacturing and provides the central hub for Aspen API's production of estrogenic hormones. The plant is a modern, automated, multi-purpose factory used for larger production campaigns with reaction vessels. API sieving, milling and micronization operations are also located at the site, together with Aspen API's central warehousing and distribution operations.

Moleneind

Oss, The Netherlands

The Moleneind production site supports a wide range of API production activities, including peptide manufacturing, Heparin manufacturing and small-scale chemical manufacturing.

Biochemical operations Boxtel

Boxtel, The Netherlands

This dedicated facility processes urine from pregnant women into the final API Chorionic Gonadotrophin (hCG)*.

**hCG is not regarded as an EDC; biodegradability is currently under investigation*

monitor the waste water of our current operations while taking steps to remain within safe levels in our treated wastewater streams.

We calculate potential environmental risk for ethinyl estradiol to determine potential adverse effects on the environment. We divide environmental risk into four different categories, depending on the ratio between the predicted environmental concentration (PEC) that determines how much of the pharmaceutical is expected to be found in the environment, and the predicted no effect concentration (PNEC), the level that is safe for wildlife[9]. The PNEC is estimated by dividing the lowest value for toxicity with the relevant assessment factor, as outlined by the European Chemicals Agency and European Medicines Agency[10]. The PEC is calculated using a worst-case scenario, assuming no removal or degradation of the API during sewage treatment.

Aspen API's wastestreams for ethinylestradiol production are equivalent to PEC/PNEC 0.11 <1, meaning that the use of the substance is considered to result in a low environmental risk[11].

[9] *https://echa.europa.eu/support/guidance*

[10] *https://echa.europa.eu/support/guidance*

[11] *Environmental Toxicology and Chemistry, Vol. 31, No. 6, pp. 1396–1406, 2012*

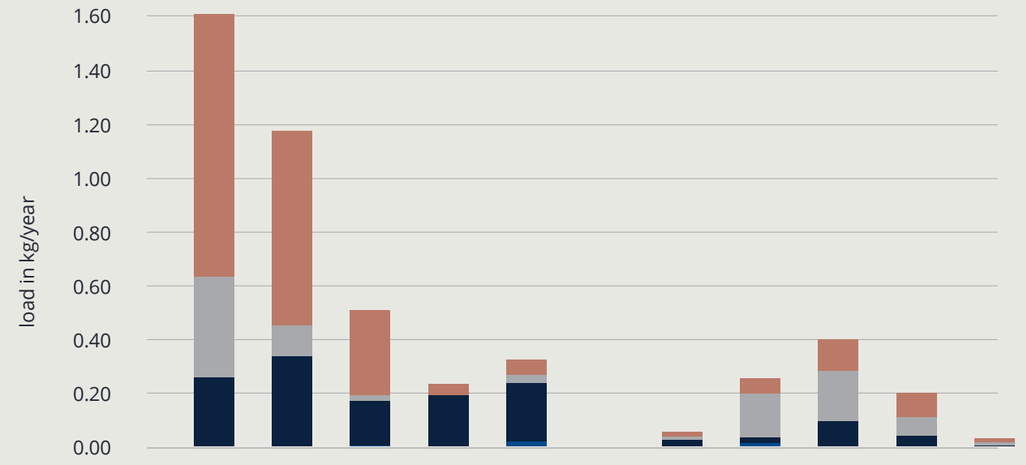
Wastewater emissions

Aspen API takes rigorous steps to prevent and reduce emissions of estrogen and other EDC residuals to water. Our approach supports the UN Sustainable Development Goals, namely Goal 6: Ensure access to water and sanitation for all, and Goal 14: Conserve and sustainably use the oceans, seas and marine resources.

Our chemical production plants in the Netherlands, including containment pits, have been disconnected from the main sewage system, preventing discharges of potentially harmful materials into the surrounding environment. All processed water streams from our Dutch facilities are connected to an above-ground collection system, known as a process water sewer, and are subsequently discharged into a collection tank. At our De Geer chemical manufacturing site in Oss, the Netherlands, the contents of the collection tanks are transported to our Moleneind manufacturing site, where they mix with process water from this facility.

Process water collected at Moleneind is evaporated and then condensated at a specialized water treatment facility, before being discharged to the sewage system. API material is removed from the effluent during the condensation process, due to the fact that APIs are non-volatile. The remaining API material is discarded as hazardous waste and incinerated.

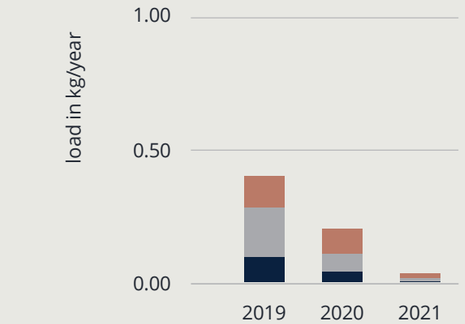
Figure 2: Estrogen discharges to wastewater at de Geer 2011-2021



	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Estron	0.97	0.72	0.31	0.04	0.05	0.00	0.02	0.05	0.11	0.09	0.01
Ethinyl Estradiol	0.37	0.12	0.02	0.00	0.03	0.00	0.01	0.16	0.19	0.07	0.01
17ß-Estradiol	0.26	0.34	0.17	0.20	0.22	0.00	0.03	0.02	0.10	0.04	0.01
17a-Estradiol	0.00	0.00	0.01	0.00	0.02	0.00	0.00	0.02	0.00	0.00	0.00

Source: Aspen API

Figure 3: Estrogen discharges into wastewater at de Geer 2019-2021 (close-up of relevant years from Figure 2)



	2019	2020	2021
Estron	0.11	0.09	0.01
Ethinyl Estradiol	0.19	0.07	0.01
17ß-Estradiol	0.10	0.04	0.01
17a-Estradiol	0.00	0.00	0.00

Source: Aspen API

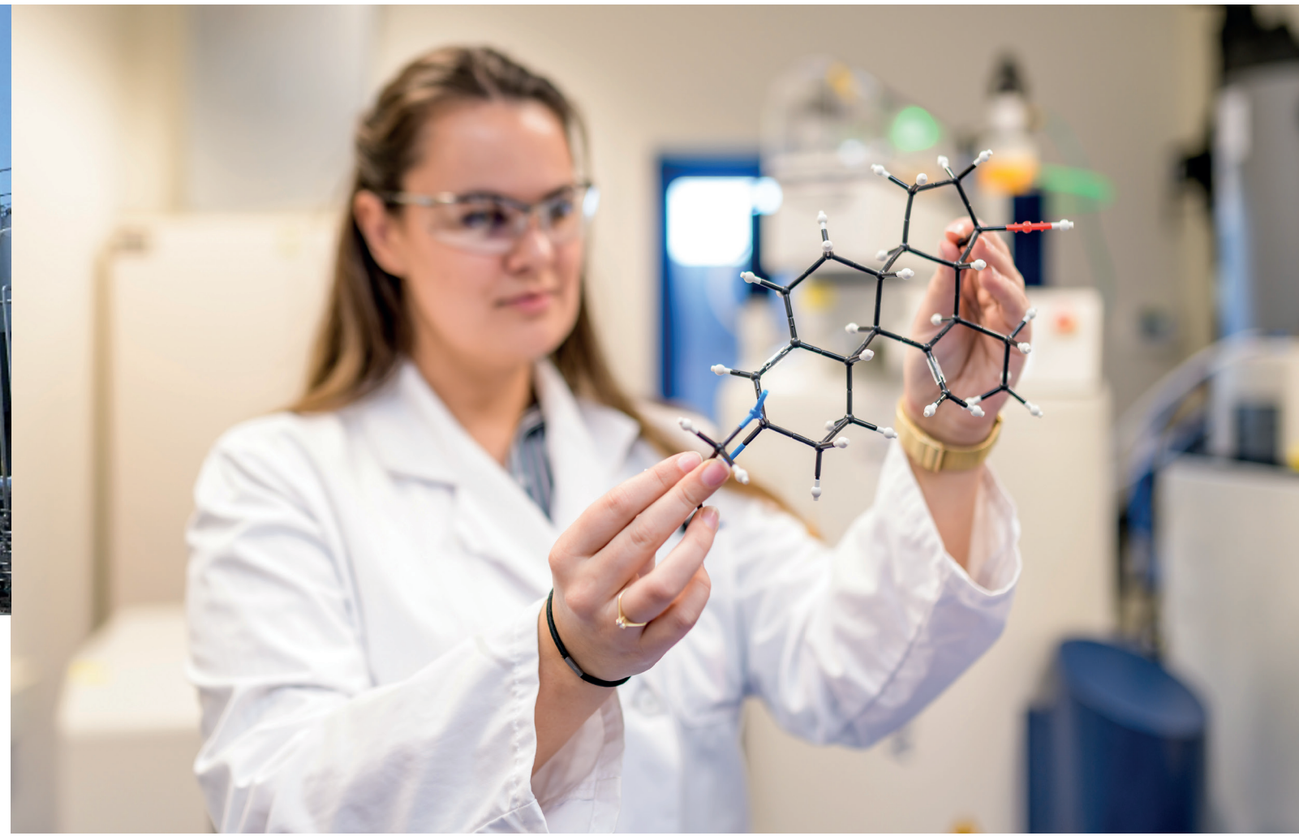
Evaporator building where exhaust air is collected and filtered

As shown by Figures 2 and 3, the introduction of this process has resulted in a more than 98% reduction in estrogen discharges to wastewater at our De Geer production facility since 2011, based on analysis of water samples taken every four weeks.

Airborne emissions
Aspen API restricts dry powder handling to a limited number of ventilated rooms within our manufacturing facilities. Wherever possible, these processes are executed in closed systems. Exhaust air is collected and filtered by a series of filters, ultimately by HEPA filtration. Emissions to air are consequently reduced to zero.

Our wider impact
In line with the recommendations of the HCWH, Aspen API strives to incentivize and support our supply chains and the wider pharmaceuticals value chain in ensuring safe and environmentally friendly operations across the entire product lifecycle. We strongly encourage customers to develop different dosage forms that result in an improved ratio of pharmaceutical use versus excretion. Furthermore, we support drug-marketing authorities by assessing the environmental risk of our medicines. We also support industry and government efforts to promote safe pharmaceuticals through initiatives such as public awareness and educational programs.

Conclusion



Advancing EDC production best practice – internally and externally
Preventing the environmental contamination of hormone-based APIs remains a key area of focus for Aspen API going forward. As a leading producer in this growing field, we are committed to tackling this serious health and environmental issue, both directly within our manufacturing facilities and, more widely, through our partnerships and interactions with the wider pharmaceuticals value chain. In particular, we are working with like-minded organizations in the Netherlands, including research institutes and government agencies, to investigate new ways to strengthen the ambitions and resulting approaches of local industry and society to limit the impact of pharmaceuticals on the environment.

For more information about Aspen API's efforts in this space as well as our wider sustainability programs, please visit www.aspenapi.com/

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