OCTOBER 2019
NATIONAL ALLERGY RESEARCH CENTRE

SOCIOECONOMIC CONSEQUENCES OF FRAGRANCE ALLERGY

FINAL

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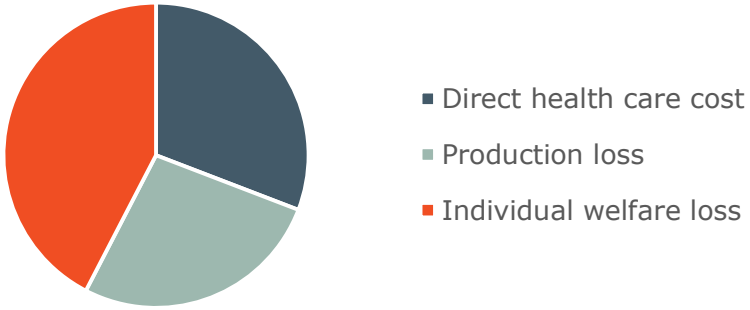
0 Summary/abstract

The current study has assessed the socio-economic consequences of fragrance allergy related to application of cosmetics in the general population in Denmark. Results have also been extrapolated to EU28. It has been commissioned by the National Allergy Research Centre (NARC) and the assessment has been carried out by COWI A/S in close cooperation with NARC.

The study estimates the costs of an average case of fragrance allergy at 182,000 DKK or 24,000 EUR. The following types of socio-economic costs are included: direct health care costs (at General Practitioners (GPs), dermatologists and hospitals), indirect productivity loss (due to patients being absent from work) and the intangible welfare loss to the individual patient and his/her family (the patient's willingness to pay for avoiding all symptoms). The costs of 182,000 DKK cover the discounted sum over the remaining lifetime of the average fragrance allergy patient. The distribution by cost elements is illustrated below.



Based on an estimated prevalence of around 5%, meaning that in Denmark around 150,000 adults suffer from fragrance allergy (have symptoms), the total socio-economic costs amounts to 1.5 billion DKK per year (0.2 billion EUR per year). Extrapolated to EU28 and assuming prevalence at 4% to 6% of the EU28 population, the annual EU28 costs of fragrance allergy are estimated at a range from 11 to 16.4 billion EUR.

1 Introduction

1.1 Background

The current study focuses on the socio-economic consequences of fragrance allergy related to application of cosmetics in the general population.

The study has been commissioned by the National Allergy Research Centre (NARC) and the assessment has been carried out in close cooperation with NARC.

Fragrance allergy and other similar allergies are diagnoses that affect a large share of the population. Therefore, it is relevant to assess the socio-economic effects and determine their significance. Fragrances in cosmetics are currently regulated at EU level through the Cosmetics Regulation (EC 1223/2009). There are ongoing discussions about whether requirements for labelling of products containing fragrances shall be extended and whether the use of certain fragrances shall be restricted.

The current study provides input to understanding the problem of fragrance allergy by estimating the socio-economic effects of fragrance allergy. Thereby, the study can provide input to policy discussions and assessments.

The report presents the assumptions, input, calculations and results of the study. Assessments are made for the Danish population and a rough extrapolation to the EU population is presented.

1.1.1 What is fragrance allergy?[1]

Fragrance allergy is an acquired immunological disorder in which an individual develops hypersensitivity, known as contact allergy, to one or more allergenic fragrance chemicals.

The development of contact allergy to a fragrance chemical involves two phases:

1 The sensitization phase, with no clinical symptoms, where the immune system is primed and matured to react to the specific fragrance chemical, resulting in sensitization of the individual.

2 The elicitation phase, which occurs upon re-exposure to the same or a structurally similar fragrance chemical. This re-exposure results in activation of the immune system, causing an allergic reaction, which manifests with clinical symptoms in the form of eczema, or more specifically allergic contact dermatitis.

[1] This and the two sections following have been written by NARC

1.1.2 Allergenic fragrance substances

More than 2700 chemicals and natural extracts are registered for use as fragrance substances in cosmetics within the EU[2]. In 2012, a comprehensive review on the topic of fragrance contact allergens in cosmetic products was published as an opinion by the Scientific Committee on Consumer Safety (SCCS) of the European Commission[3]. The SCCS opinion identified 82 fragrance substances that were categorized as established contact allergens in humans. Since 2005, 26 of these fragrance substances have been mandatory to label in cosmetic products within the EU if present at 10 ppm or above in leave-on and 100 ppm or above in rinse-off cosmetics[4]. The 26 fragrance substances are only to be labelled by their name, with no information provided on their use concentrations.

1.1.3 Diagnosing fragrance allergy

Fragrance allergy is diagnosed by patch testing with both general and specific series of contact allergens. The European baselines series of contact allergens includes two mixtures of known fragrance allergens: Fragrance mix I (FMI), comprised of seven fragrance chemicals and one natural extract and Fragrance mix II (FMII) consisting of six fragrance chemicals. All 14 fragrance substances in the two mixes are among the 26 fragrances with mandatory labelling in cosmetics. In addition, the European baseline series contains the fragrance chemical hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, which is also a component of FMII) and the natural extract Balsam of Peru (Myroxylon pereirae). The latter has, at least historically, often been used as a marker for fragrance allergy[5].

1.2 Objective of this study

The main objective of the study is to estimate the burden and socioeconomic consequences of fragrance allergy in the Danish population. Additionally, the objective is to consider the socioeconomic effects at the European level and based on an extrapolation of the costs for Denmark providing an estimate of the costs of fragrance allergy for EU28.

1.3 Overall approach

Based on the best available scientific knowledge on the incidence and prevalence of fragrance allergy combined with knowledge on the typical diagnose and treatment processes, the study estimates the number of patients diagnosed with fragrance allergy and the subsequent number of patients in different categories of treatment. For each person being diagnosed, the socio-economic costs are assessed allowing the estimation of aggregated costs at a national level.

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[2] (European Commission, 2018)

[3] (Uter, Johansen, Börje,, & al., 2013)

[4] (SCCNFP/0017/98, 1999)

[5] (Scheman, Rakowski, Chou, & al., 2013)

In short, the approach comprises the followings steps:

- Estimation of the annual number of people being diagnosed by each treatment level
- Assessment of the treatment activities for each treatment level
- Estimation of costs

The analysis has been set up in a calculation model allowing for assessing the different outputs such as costs of one case, annual costs and future costs.

For each phase of diagnose or treatment stage, the model describes the health care system activities and the associated costs. The model includes three types of costs[6]:

- Direct health care costs (General Practitioners (GP), specialist (e.g. dermatologists), hospitals, medicine etc.)
- Indirect productivity loss (loss of production value due to absence from work)
- Intangible costs to the patient caused by the symptoms of fragrance allergy (welfare loss which in this study will be assessed based on the patient's willingness to pay for avoiding the symptoms)

These three cost types constitute the main socio-economic consequences of fragrance allergy. Other direct and derived costs from fragrance allergy such as private cost of visiting health care professionals (e.g. transport to the clinic, lost time etc.), home environment modifications (use of fragrance-free products), reduced productivity in terms of presenteeism and loss incurred by job changes are not included.

For the additional private costs such as the transport costs to the health clinics and hospitals, they are considered quite small compared to the other elements and they could be included in the assessment of intangible costs. Additional productively loss due the effects of the allergy for patients going to work is very difficult to assess. There are no data and the main part of the loss of productivity is captured through the increased sick absence from work. The only effect left out of the assessment that could potentially be significant is if patients have to change job. Job change would entail costs of the individual in terms of loss of income and costs to society in terms of lost production value.

Overall, we assess that the omitted elements are minor socioeconomic costs, but it means that our cost assessment of the socioeconomic effects is conservative in the sense that it may slightly underestimate the true costs.

The results of the assessments - using our cost model - are presented in four different ways:

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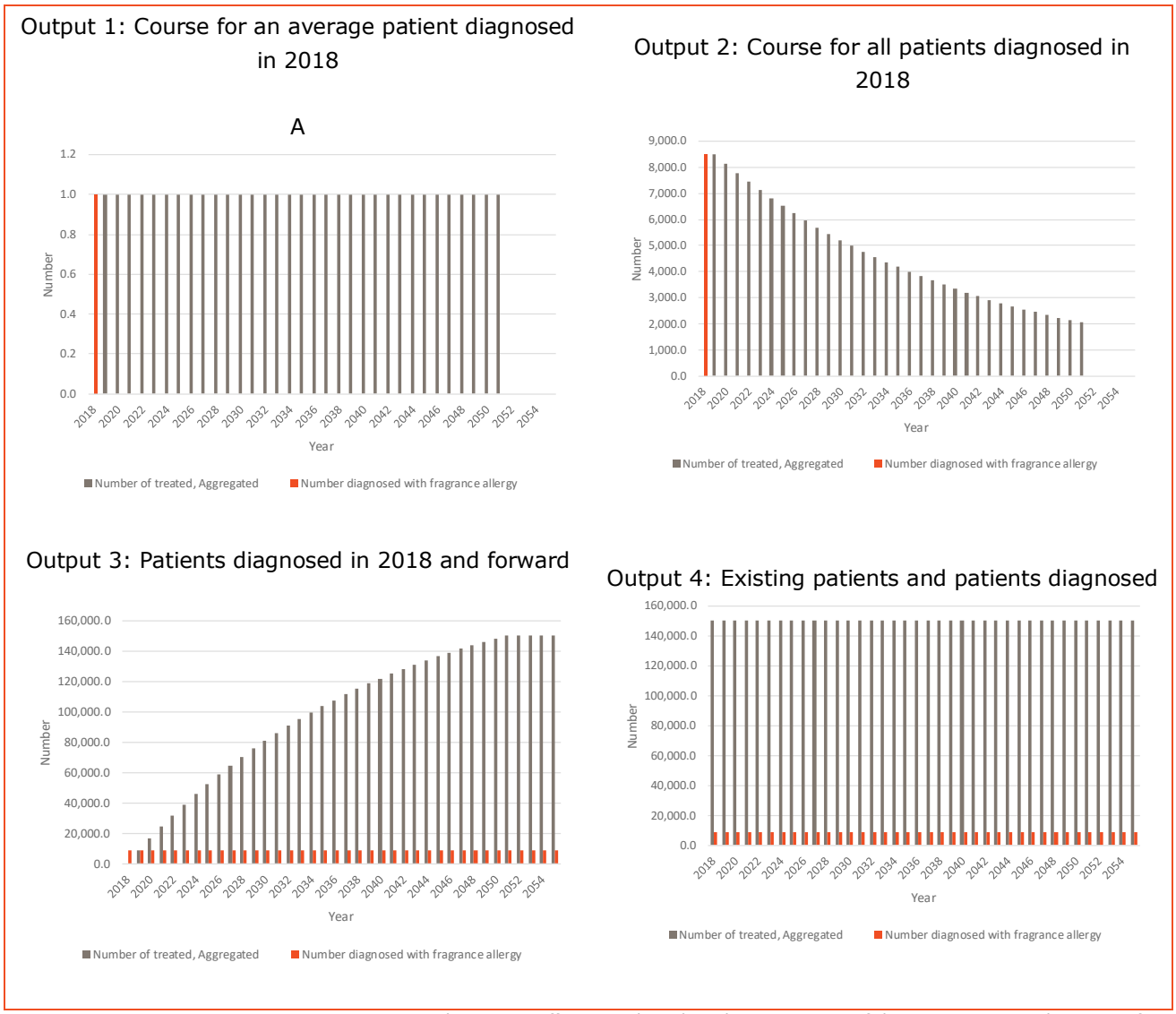
[6] In economic valuation studies, it is common to distinguish between direct and indirect costs. Here, we further divide the indirect costs into productivity loss and the intangible welfare loss, see for example (Sørensen, Gudum, & Serup-Hansen, 2004)

- Output 1: Average socio-economic consequences for one single case of fragrance allergy
  - the social costs over lifetime of one person being diagnosed at an average age of 49
- Output 2: Socio-economic consequences of fragrance allergy for patients diagnosed in 2018 (single cohort)
- Output 3: Socio-economic consequences of fragrance allergy for patients diagnosed in 2018 and beyond
  - costs that could be affected by changing the exposure and reducing the number of new diagnoses
- Output 4: Socio-economic consequences of fragrance allergy incl. current treatment of patients diagnosed before 2018
  - total costs of all persons that have a diagnose over an assessment period of 50 years.
- Output 5: Socio-economic consequences of fragrance allergy incl. current treatment of patients diagnosed before 2018
  - total annual treatment and diagnose costs of all persons that have a diagnose (prevalence) or are being diagnosed in one year

Figure 1-1 shows the number of diagnosed (new cases) and treated (patients with fragrance allergy) per year according to the model outputs. Output 1 shows one person diagnosed in 2018 that continue to have the diagnose for the rest of the person's life. Output 2 illustrates all adults being diagnosed in 2018 and how many will continue to have symptoms over the rests of their life. As it will be discussed in this report, though fragrance allergy is permanent, some patients will over time be free of symptoms. Output 3 illustrates the number of people diagnosed with fragrance allergy starting from 2018 onwards. As every year more people are being diagnosed, the number will increase over time in this Output 3 model. This increase will slowly by offset by the fact that some will be free of symptoms overtime. The average age at being diagnose is assumed at 49 and with average expected remaining lifetime of 33 years, around 2050, the number will stabilise for the Output 3 model. Output 4 includes all those who have already been diagnosed. As no trends are assumed for neither the size of the population nor the share being diagnosed, the total number of people with diagnose and symptoms remains constant over time in the Output 4 model. Output 5 is not illustrated as it is one year of what is shown in Output 4. When assessing the costs related to the five outputs, Outputs 1 to 4 assume costs over a 50-year assessments period being discounted to a net present value, while Output 5 is the annual costs related to all existing patients and those being diagnosed in one year. It means that Output 5 describes the total annual costs to society of fragrance allergy.

Figure 1-1 Output 1 – 4, number of diagnosed and treated per year, shown for the period 2018-2055



Note: Figure 1 and 2 are cut off at 2051 based on the assumption of the average patient being 49 of age at time of being diagnosed and having remaining lifetime of 33 years. Figure 3 and 4 are cut-off at year 2055, since this correspond a steady state for all four model outputs. For Output 3 and Output 4 number of treated are rising with the number of diagnosed and reduced with the number of patients experiencing a reduction in symptoms and patients dying of age

2 Methodology

This chapter explains the approach and presents the inputs and assumptions used for modelling the socioeconomic consequences of fragrance allergy.

2.1 General approach

The approach comprises the followings steps:

- Estimation of the relevant population
  - Annual number of new cases with adults experiencing fragrance allergy
  - Number of adults undergoing treatment for fragrance allergy by different levels of severity and associated treatment level
- Assessment of diagnosis activities
  - Estimation of costs for diagnosis activities
- Assessment of the treatment activities for each treatment level
  - Estimation of costs for treatment activities
- Total cost assessment based on number of cases at different treatment levels and costs per case.
  - Costs assessment for Denmark followed by extrapolation to an estimate for EU28.

As described in Section 1.3, the analysis has been set up in a calculation model allowing for assessing the different outputs such as costs of one case, annual costs and future costs.

2.2 Number of fragrance allergy cases

The first step in the analysis is to calculate the relevant number of fragrance allergy cases.

The numbers that can be estimated based on the available studies and data are the annual number of people being diagnosed with fragrance allergy through consultation with a dermatologist and the total number of people that live with fragrance allergy.

The annual number being diagnosed are based on data recorded by dermatologists. The prevalence, the estimated number of people in the whole population that have fragrance allergy are based on a recent European population investigation[7].

2.2.1 Annual number of new cases

Our assessment is anchored in the estimate of annual number of new diagnosed being made by the dermatologist.

[7] (Diepgen TL, 2015)

The individual diagnosis process might be different, where some patients might be diagnosed early in the process while others might have several visits to dermatologist and hospitals.

Based on dialogue with specialists, we have found it reasonable to divide and categorise the diagnosis process in a number of steps, each being a possible endpoint for the treatment[8]:

1 The individuals will decide whether to take action upon their symptoms, some individuals will take no action and live with their symptoms (endpoint: No action).

2 Taking action will necessitate consulting own general practitioner (GP), who will suggest treatment e.g. prescribe moisturizer and topical corticosteroids (endpoint: GP). Depending on the individual case, the GP might refer the patient to a dermatologist.

3 The patient will be examined, tested and treated by the dermatologist (endpoint: Dermatologist). If no diagnosis can be made or the case requires special treatment, then the individual will be referred to hospitals.

4 Finally, the patient will be examined, tested and eventually diagnosed at the hospital. Depending on the case the patient might also be treated at the hospital (endpoint: Hospitals).

Figure 2-1 and Table 2-1 list the number of new cases with fragrance allergy. Our estimates of the four typical endpoints are based on the annual number of patients diagnosed at the dermatologist. 3,750 Danish patients are diagnosed with fragrance allergy annually[9]. This estimate is based on the estimated number of patch-tested patients in Denmark yearly (n=25.000)[10] and investigations showing that 15% are diagnosed with fragrance allergy[11]. It is estimated that 10 % of these are referred to a hospital for further diagnosis. This estimate is based on data from The National Clinical Database for Contact Allergy covering all hospital departments in Dermatology and a selection of private practices[12].

To estimate the number of patients with fragrance allergy that have not been referred from their own GP or are living with their symptoms, we use the study by (Hald M, 2008). The study suggests that 44% of the population with hand eczema are referred to a dermatologist. This is then used to estimate the annual number of those being sensitized with symptoms (8,523)[13]. 67 % of the sensitized population are going to their own GP according to (Hald M, 2008),

[8] This reflects the current Danish health practice for the typical diagnose process

[9] (NARC, 2019)

[10] (Thyssen JP1, 2007)

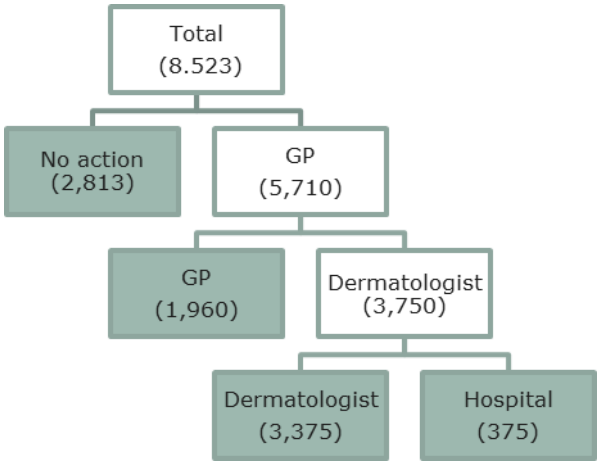
[11] (Bennike NH, 2017)

[12] https://www.videncenterforallergi.dk/allergiovervaagning/om-den-kliniske-database/

[13] 3750 divided by 0.44 gives 8523.

which yield the number of cases consulting the GP (5,710) and those living with the symptoms without such consultation (no action). Only patients diagnosed by either a dermatologist or through examination in hospitals are diagnosed with fragrance allergy[14], and the endpoint with *no action* and *GP* thus represents shadow figures.

Figure 2-1 Annual number of new cases with fragrance allergy (green boxes indicate endpoint)



Source: Expert assessment by NARC, (Hald M, 2008), (NARC, 2019)

Table 2-1: Annual number of new cases with fragrance allergy

	New cases with fragrance allergy, total	New cases with fragrance allergy, by endpoint
No action	2,813	2,813
GP	5,710	1,960
Dermatologist	3,750	3,375
Hospital	375	375
Total	**8,523**	**8,523**

Source: Expert assessment by NARC, (Hald M, 2008), (NARC, 2019)

The total number of new cases with fragrance allergy are set to undergo treatment the following year. Patients are divided into five different treatment groups (from *few symptoms and no treatment* to *severe dermatitis with frequent eruptions*) after the severity of the individual's fragrance allergy condition[15]:

- Treatment group 0 is consisting of people living with fragrance allergy without having consulted their general practitioner. People in this groups will usually have few or no symptoms. The number in this group is 2,813 as it is the same number as those with no action (see Table 2-1).

[14] Expert assessment by NARC

[15] Expert assessment by NARC

- Treatment group 1 is patients with no chronic eczema but frequent eruptions or light chronic dermatitis. This group comprise 2/3 of those visiting their GP (as endpoint; see Table 2-1) combined with one-third of those visiting a dermatologist (as endpoint; see Table 2-1). The number is 2427.

- Treatment group 2 and 2+ are patients experiencing moderate to severe dermatitis with either seldom or frequent eruptions. Group 2 and 2+ comprise one-third of those visiting their GP, two-thirds of those visiting a dermatologist and two-thirds of those visiting a hospital (all as endpoints; see Table 2-1). This amounts 3160 patients out of which 80% is assigned to group 2 and 20% to group 2+.

- Treatment group 3 are patients experiencing severe dermatitis with frequent eruptions. Group 3 comprise one-third of those visiting the hospital as endpoint (see Table 2-1) and it is estimated to 124 patients.

The distribution by the different treatment groups is based on an expert assessment by NARC. The severity of fragrance allergy will usually be corelated with the given diagnosis endpoint. In general, more severe cases of fragrance allergy are expected at the dermatologist and hospital rather than at the GP and by self-treatment. The assumptions on the relation between the endpoint of the diagnose process and the treatment groups are summarised in Table 2-2.

Table 2-2: Assumption on the division on treatment group

	Endpoint 1: No action	Endpoint 2: GP	Endpoint 3: Dermatologist	Endpoint 4: Hospital
Treatment group 0	100%			
Treatment group 1		67%	33%	
Treatment group 2		0,8 * 33%	0,8 * 67%	0,8 * 67%
Treatment group 2+		0,2 * 33%	0,2 * 67%	0,2 * 67%
Treatment group 3				33%
Total	**100%**	**100%**	**100%**	**100%**

Source: Expert assessment by NARC

As it can be seen in the above table, the distribution by treatment group is based on the estimate that 2 out of 3 patients seen by the GP have light symptoms and 1 out of 3 have moderate to severe symptoms. Furthermore, in those referred to dermatologist, 1 out of 3 will have light symptoms and 2 out of 3 will have moderate to severe symptoms. All cases seen in hospital departments are considered moderate (2/3) to severe (1/3).

These assumptions are conservative, considering that data from investigations of patients diagnosed with fragrance allergy[16], showing that most Danish

[16] See (Lysdal SH, 2009) and (Bennike, et al., 2019)

fragrance allergic patients (82.1%)[17] reported some degree of eczema after diagnosis and that 42.7% had eczema at multiple locations[18]. In a similar European investigation covering 4 countries, 47% had current eczema and 13% within the past week[19].

Based on the assessment and assumptions described above, Table 2-3 includes the resulting distribution of the annual number of new cases with fragrance allergy by treatment group. It means that those in treatment group 1 to 3 will start a treatment process in the year after being diagnosed.

Table 2-3: Patients in treatment, year 1

Treatment group	Number of patients, Single cohort
Treatment group 0	2,813
Treatment group 1	2,427
Treatment group 2	2,528
Treatment group 2+	632
Treatment group 3	124
Total	**8,523**

Source: Table 2-1 and Table 2-2
Note: Number of patients per group (Table 2-1) is divided according to Table 2-2

The assessment of the costs associated with fragrance allergy is using the above estimated number of patients by treatment group (Table 2-3). For some patients the symptoms are slowly decreasing over time. Hence, the number of patients from a single cohort is expected to decrease over time. We assume a constant reduction in the number of treated of approx. 4.4 % per annum. This is based on a study where it was possible to compare the share of eczema patients with symptoms over time. The result indicated that 64 % of eczema patients (which fragrance allergy belongs to) were still experiencing symptoms after 10 years (Bregnbak, Thyssen, Zachariae, & Johansen, 2014).

2.2.2 Prevalence assessment

As mentioned above, the cost estimation is primarily based on the annual number of new cases, which is like an incidence figure. The assumptions we use to assess the current burden of disease is using estimates of prevalence numbers.

Table 2-4 shows the assumptions used for modelling the total sensitized population. The total sensitized population is a steady state determined by the number of new cases with fragrance allergy, average life expectancy when diagnosed with the disease and the annual reduction of people with symptoms

[17] (Lysdal SH, 2009)
[18] (Lysdal SH, 2009)
[19] (Bennike, et al., 2019)

due to either end of their lifetime or the assumed annual reduction of 4.4% of those with symptoms.

The diagnose can be made at any age. At the age of 16, it is estimated that 2.4% are allergic to common fragrance ingredients[20], however it may take a long while before the diagnosis is made. The typical age where people are being diagnosed are in the late 40ies or early 50ies. We assume that the average age of being diagnosed is at age of 49. For the calculation, the costs per one new case are therefore estimated for the remaining lifetime, which is 33 years. In this calculation we disregard the effect and costs in the younger age groups. For the indirect costs related to productivity loss, the costs are counted up to the pension age, which is assumed at 70 years of age meaning that the productivity loss is estimated for 21 years per case.

Table 2-4: Population parameters

	Unit	Value	Source
Annual decrease in number of treated	%	4,4 %	(Bregnbak, Thyssen, Zachariae, & Johansen, 2014)
Age, when the symptoms typically begin	Year	30	(Bennike, et al., 2019)
Age, when people typical is diagnosed	Year	49	(Bennike, et al., 2019)
Life expectancy at 49 years old	Year	33	(Danmarks Statistik, 2019)
Pension age	Year	70	(STAR, 2019)

The annual decrease in the number of treated combined with the annual number of diagnosed and the life expectancy yields an annual population estimate of approximately 150,000 people in steady state experiencing symptoms related to fragrance allergy, see Table 2-5.

Table 2-5: Annual total number of patients in treatment, steady state

	Number of patients – Current burden of disease
Treatment group 0	49,660
Treatment group 1	42,855
Treatment group 2	44,628
Treatment group 2+	11,157
Treatment group 3	2,185
Total	**150,485**

Source: Own calculations based on Table 2-3 and Table 2-4

Proportion of population sensitized

A study by (Diepgen TL, 2015) suggests that 4.1% of the population is sensitized for fragrance allergy; however, their study is based on tests of a limited number of fragrances. If more fragrance allergens are used for testing, around 1/3 more allergies are likely to be detected[21]. Based on this it is estimated that a share of 6% for Denmark would be appropriate if more

[20] (Lagrelius, Wahlgren, Matura, Kull, & Lidén, 2016)

[21] (Bennike NH, 2017) and (Mann, McFadden, White, White, & Banerjee, 2014)

fragrance allergens are considered. With a Danish population of approx. 4.6 million people above 18 years of age[22] and combining the assumption that 63% of the population that are sensitized for fragrance allergy experience symptoms (Diepgen TL, 2015) yields an estimate for a sensitized population with symptoms of approx. 175,000. The next table shows the number of sensitised under alternative assumptions on the share of the population - the estimated prevalence - that are sensitized. The table includes both the total number of sensitized and the number which experiences symptoms.

Table 2-6 Estimated prevalence numbers

Number of sensitized	Proportion of population sensitized		
	4%	5%	6%
Number of sensitized	189,000	233,000	277,000
Number of sensitized with symptoms	119,000	147,000	174,000

Source: Own calculations based on the alternative shares being sensitized and share with symptoms being 63% of those sensitized.

The prevalence number we have estimated using the data on the annual number of new cases and remaining lifetime for those being diagnosed is approximately 150,000 (see Table 2-5). Hence, the estimated number of sensitized with symptoms coming from our model is equivalent to a prevalence of around 5%. This suggests that our model is a conservative estimate of the prevalence (using around 5%), as the best estimate for the Danish population as argued above is a prevalence number of 6%.

2.3 Direct health care costs

2.3.1 Diagnosis activities and their costs

People experiencing symptoms from fragrances and scented products can be treated and diagnosed through contact with the national health care system.

This diagnostic process and the relevant courses and endpoints are based on the data and estimates explained above in relation to Tables 2-2 and 2-3.

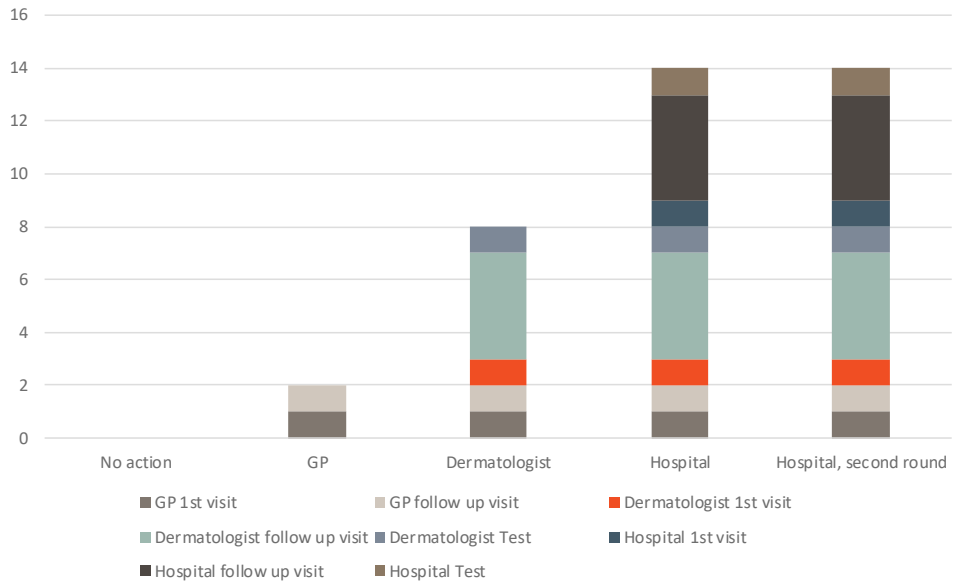
A course describes the process from consultations to endpoints. The first course is people experiencing minor or mild symptoms that disregard going to their general practitioner (GP) in the first place. This means that the endpoint is no action (see Figure 2-1). The second course is people visiting their GP, where we assume a 1st visits and a follow-up visit, before either being symptom-treated or referred to a dermatologist. The third course is people who have been referred from their GP and are being diagnosed at the dermatologist. The fourth course consist of the relatively small number of people where no diagnosis could

[22] Population above 18 years: 4,615,690 (Danmarks Statistik, 2019)

be given by the dermatologist, and where the patients therefore have been referred to a hospital. The four courses for people with fragrance allergy therefore represent an increasing number of visits to health care professionals and testing, where the fourth course has the highest number of contacts and testing.

Figure 2-2 shows the assumed number of visits and tests at the GP, the dermatologist and/ or hospital for people with fragrance allergy divided by endpoint.

Figure 2-2 Number of visits and test per endpoint



Source: Expert assessment by NARC 2019

Cost of diagnosis

The cost of a diagnosis includes all activities related to diagnosing the patient. This is done at the GP, dermatologist and at the hospital ambulatory. Direct costs depend on the specific course. The costs of a visit to the GP is estimated at about 142 DKK per visit and the costs increase for visits to the dermatologist and to the hospital as shown in Figure 2-2.

Table 2-7: Expected unit cost of GP, Dermatologist and Hospital service

	Unit	Value	Source
GP			
Consultation	DKK / visit	142	(Honorartabel, 2018)
Dermatologist			
1. Consultation	DKK / visit	515	(Takstkort Dermatologi, 2018)
Follow up consultation	DKK / visit	156	(Takstkort Dermatologi, 2018)
Patch test	DKK / test	246	(Takstkort Dermatologi, 2018)
Light treatment (UV)*	DKK / Light treatment (UV)	2,346	(Takstkort Dermatologi, 2018)
Hospital out-patient clinic			
MDC091-daygroup, patient min. 7 years (09MA98)	DKK / visit	1.774	(Sundhedsdatastyrelsen, 2019)

Note *: Light treatment (UV), given at the dermatologist, patient has to go 3 times á week for 4 weeks – 10 weeks (6 weeks chosen as mean) based on an expert assessment by NARC. Treatment cost per visit is estimated as price of follow-up consultation. Light treatment (UV) are only provided to treatment group 2+.

Table 2-8 shows the services and activities related to diagnosing the patient, and the aggregated unit costs per endpoint.

The annual follow-up visits after diagnosis and resulting unit cost per treatment group is given later in Table 2-15.

Table 2-8: Aggregated unit costs (DKK), 2018

		Endpoint/course			
Specialist	Unit	No action	GP	Dermatologist	Hospital
GP	1st visit	-	142	142	142
	follow up visits	-	142	142	142
Dermatologist	1st visit	-	-	515	515
	follow up visits	-	-	626	626
	Tests	-	-	721	721
Hospital	1st visits	-	-	-	1,744
	follow up visits	-	-	-	6,976
Total		**0**	**285**	**2,146**	**10,866**

Source: Own calculations based on Table 2-7

Direct total cost of consultations at the GP are estimated at DKK 285. These direct costs will be related to consultation and diagnosing all patient in course 2 - 4. Direct total cost of consultation and diagnosis at the dermatologist are estimated at DKK 1.861, incl. additional cost for light (UV) treatment and when adding the costs of visits to the GP, the total direct costs of getting the diagnose is estimated at 2146 DDK per patients that has the dermatologist as endpoint. Direct total cost of diagnosis at the hospital ambulatory is estimated at DKK 8.720 for patients in course 4. When including costs of GP and dermatologist, direct total costs of establishing the diagnosis are DKK 10.866 for endpoint/ course 4.

2.3.2 Treatment activities and their costs

The cost of treatment is besides severity of the fragrance allergy based on the type and multitude of eczema. Table 2-9 list the expected types of eczema for the fragrance allergist divided in hand, face and multiple location eczema.

Table 2-9: Type of eczema

	Hand eczema	Facial eczema	Multiple location eczema
Value	33%	33%	33%

Source: (Lysdal SH, 2009)

Cost of daily treatment

Costs of daily treatment reflect the average use of lotions, preventive and soothing medicine, supplies, as well as routine visits to the dermatologist within a year. Supplies covers private use of disposable and cotton gloves. Medicines covers corticosteroid cream and medicine related to systemic treatment. Based

on information on the type of treatment from the Danish National Allergy Research Centre, costs can be estimated per treatment group, see Table 2-10 for a description of treatment per group.

Table 2-10: Description of treatment

	Description
Treatment group 0	None
Treatment group 1[1]	Hand eczema or facial eczema: › Moisturizer: 50g / week › Corticosteroid cream: 3 x 50g / year › For hand eczema: 35 pairs of disposable gloves á week. Cotton gloves 10 pair per month.
Treatment group 2 and 2+[1]	Hand eczema or facial eczema: › Moisturizer: 50g / week › Corticosteroid cream: 5 x 50g / year › For hand eczema: 35 pairs of disposable gloves á week. Cotton gloves 10 pair per month.
Treatment group 3	Multiple locations: › Moisturizer 50 g/week; › Corticosteroid cream: 6 x 50g / year › Gloves 35 pairs á week. Cotton gloves 10 pair per month. › Additionally, systemic treatment for 25% of the group *Methotrexate used in the calculations, as the cheapest option.*

Source: Expert assessment by NARC
Note 1: Double up on corticosteroid cream and moisturizers for both hand and face eczema

The following table shows the unit prices per type of treatment.

Table 2-11: Unit prices for treatment parameters

	Unit	Value	Source
Moisturizers	(DKK/g)	0.6	(Webapoteket.dk, 2019) (Matas.dk, 2019)
Corticosteroid cream	(DKK/g)	4.5	(Medicinpriser, 2019)
Gloves, disposable nitrile	(DKK/p)	0.7	(Matas.dk, 2019)
Gloves, cotton	(DKK/p)	2.0	(Grafical.dk, 2019)
Methotrexate	(DKK/mg)	1.1	(PRO.MEDICIN, 2019)

Note: Moisturizers and corticosteroid cream are a weighted average on a range of products recommended by NARC.

Annual treatment costs per type of treatment/product per treatment group is presented in below table. The table present the costs based on the full price of the different products.

Table 2-12 Annual treatment cost per type of treatment, DKK

	Hand eczema	Face eczema	Face and hand eczema (Multiple)
Treatment group 0			
Moisturizers	-	-	-
Treatment group 1			
Moisturizers	1,549	1,549	3,097
Corticosteroid cream	681	681	1,361
Gloves	1,274	0	1,274
Cotton gloves	240	0	240
Treatment group 2			
Moisturizers	1,549	1,549	3,097
Corticosteroid cream	1,134	1,134	1,361
Gloves	1,274	0	1,274
Cotton gloves	240	0	240
Treatment group 2+			
Moisturizers	1,549	1,549	3,097
Corticosteroid cream	1,134	1,134	2,268
Gloves	1,274	0	1,274
Cotton gloves	240	0	240
Treatment group 3			
Moisturizers	-	-	3,097
Corticosteroid cream	-	-	2,722
Gloves	-	-	1,274
Cotton gloves	-	-	240
Methotrexate	-	-	See Table 2-14

Source: Calculations based on Table 2-10 and Table 2-11

Total annual treatment cost for corticosteroid cream and medicine for systemic treatment per patient per treatment group are used as basis for calculation of national public subsidies for subsidy eligible medicine. In general, larger subsidies are provided for higher expenses to medicine; however, the maximum own-payment is capped at DKK 4,030. In turn, the public health care system will also have costs related to subsidies provided for private costs to treatment, see allocation in Table 2-13.

Table 2-13: Annual treatment cost per subgroup, DKK

	Private expenses	Public expenses (subsidy)	Total expenses
Treatment group 0	0	0	0
Treatment group 1, hand	3,743	0	3,743
Treatment group 1, face	2,229	0	2,229
Treatment group 1, both	5,774	198	5,972
Treatment group 2, hand	4,112	85	4,197
Treatment group 2, face	2,598	85	2,683
Treatment group 2, both	5,774	198	5,972
Treatment group 2+, hand	4,112	85	4,197
Treatment group 2+, face	2,598	85	2,683
Treatment group 2+, both	6,059	820	6,880
Treatment group 3	6,173	1,160	7,333

Source: (Lægemiddelstyrelsen, 2019) and COWI expert judgement
Note: Public subsidies based on expenses to corticosteroid cream and medicine for systemic treatment

A share of patients in treatment group 3 need systemic treatment for a period after diagnosis with e.g. Methotrexate. These costs are not included in the above estimates but are shown in the table below.

Table 2-14 Expenses related to systemic treatment with Methotrexate

	Unit	Year 1	Year 2
Private expenses	DKK	856	856
Public expenses	DKK	237	237
Total	**DKK**	**1,093**	**1,093**

Source: COWI based on (PRO.MEDICIN, 2019)

Table 2-15 shows the annual number of consultations at the dermatologist as expected by NARC. The direct cost associated with a visit is descried earlier (see Table 2-7). The table shows visits and costs at the first year and after 10 years.

Over time, the patients might have fewer visits to the dermatologist. For the assessment we use the assumption that the number of visits gradually decrease. We assume an annual decrease similar to the one for the share of patients that experiences symptoms. It means an annual reduction in the number of visits by 4.4%; see Table 2-4). Alternatively, as sensitivity assessment, we have estimated the costs if it is assumed that after first year visits, patients do not have visits in any of the following years.

Table 2-15: Consultations and aggregated unit costs per treatment group, 2018

	Annual consultations with dermatologist		Annual unit cost per patient (2018)	
	First year	After 10 years	First year	After 10 years
Treatment group 0	0	0.0	0	0
Treatment group 1	1	0.6	156	100
Treatment group 2	2	1.3	313	200
Treatment group 2+	3	1.9	469	300
Treatment group 3	4	2.6	626	400

Source: Expert assessment by NARC

2.4 Indirect costs

The indirect costs include the loss of production value due to people with fragrance allergy being off work. The indirect costs are estimated as the number of sick-days times the loss of production value per day.

We do not include other costs related to possible productivity loss. Such costs could include that people with fragrance allergy may go to work, but their effectiveness is reduced. In a longer term, they may have to change occupation to reduce the risk of exposure to fragrance substances or if their eczema prevents them from doing their current job. There are very limited data on these possible effects and therefore it will be too uncertain to include them in the assessment. Not having included these effects means that the assessment of the indirect costs could be an underestimation.

Production Loss

Sick leave due to fragrance allergy is assumed to be more prevalent for people diagnosed with fragrance allergy than people who are only treating symptoms (No action and GP). Table 2-16 shows the annual number of sick days according to (Saetterstrøm, Olsen, & Johansen, 2014). Table 2-17 shows the production loss per day.

Table 2-16: Reported sick leave (days)

	Unit	Value	Source
Number of sick-days, those with a diagnose	Days	5.6	(Saetterstrøm, Olsen, & Johansen, 2014)
Number of sick-days, those with no diagnose	Days	2.1	(Saetterstrøm, Olsen, & Johansen, 2014)

The value of production loss per day is estimated using the production value generated per person per day. The production value is based on the average income per person assuming the production value generated per person is reflected in the paid salary. Using the average annual production values and average number of workings per year, the production loss is estimated at DKK 926 per sick day.

The production loss per person having fragrance allergy is estimated assuming the average age of 49 when being diagnosed and then included in the calculations until the individual patient reach their pension age which is assumed as 70 years.

Table 2-17: Production loss, DKK

	Unit	Value	Source
Average disposable income	DKK	234,400	(Danmarks Statistik, 2019a) (Danmarks Statistik, 2019b)
Number of working days	Days	253	(Danmarks Statistik, 2019a)
Production loss	DKK / day	926	Calculated value

2.5 Intangible costs

Intangible cost related to fragrance allergy

In addition to the private cost of treatment, fragrance allergists will experience other intangible costs related to the annoyance and inconvenience of having fragrance allergy.

The intangible costs are assessed as the willingness to pay (WTP) for avoiding being diagnosed with fragrance allergy. The next sub-section describes the basis for estimating WTP and the assessment of the literature on WTP leading the WTP values applied in this study.

2.5.1 Willingness to pay

The intangible costs related to annoyance and inconvenience of having fragrance allergy is an important component of the social costs. Assessment of this component is inherently subject to uncertainty.

Without going into details about the general challenges of undertaking willingness to pay valuations, it should be noted that it is being accepted as the approach when considering intangible effects. Reference can be made to EHCA's guidance on socio-economic assessments under the EU chemicals regulation REACH where the assessment of the benefits in most cases require that the intangible health effects are valued in monetary units[23].

There are no studies that have specifically assessed willingness to pay of fragrance allergy. A number of studies have looked at atopic dermatitis or contact allergy as the type of diagnose considered closest to fragrance allergy.

To establish that the identified willingness to pay results are valid as approximations for the intangible costs of fragrance allergy, we have done the following:

[23] See the guidance on socio economic analysis under the REACH Restriction and Authorisation procedures: https://echa.europa.eu/support/socio-economic-analysis-in-reach

- Compared symptoms of fragrance allergy with other skin diseases
- Assessed the literature and estimated the most likely value for the willingness to pay
- Compared the WTP results from atopic dermatitis and contact allergy with estimates based on alternative approaches:
  - Estimation combining the number of days with symptoms and a WTP for avoiding days with restricted activity leading a total value of the intangible costs
  - Estimation using the quality of life index (DALY) and valuation of one life year.

Symptoms of different skin diseases

The symptoms of different skin diseases are very similar. Below we have presented the main symptoms for three diseases: fragrance allergy, contact allergy and atopic dermatitis.

Table 2-18 Symptoms for skin diseases

Disease	Main symptoms	Other symptoms
Contact allergy incl. fragrance allergy[24]	Skin becomes red, inflamed (irritated), blistered, if reactions persist the skin will become dry, thickened and cracked	Occasionally, areas of skin affected by contact dermatitis can become infected.
Atopic dermatitis	Atopic eczema causes areas of skin to become itchy, dry, cracked, sore and red	Occasionally, areas of skin affected by contact dermatitis can become infected.

Source: (Johansen, et al., 2015)

As fragrance allergy is contact allergy, the symptoms are identical and therefore, data on willingness to pay for avoiding the symptoms of contact allergy can be used as approximation for the willingness to pay for avoiding symptoms of fragrance allergy. Data for atopic dermatitis can also be used, thought the disease is more chronic and more related to genetic factors than fragrance allergy.

Overall, the comparison shows that estimations of the intangible costs for both contact allergy and atopic dermatitis can be used to approximate the costs for fragrance allergy.

The evidence on how fragrance allergy patients are affected suggests that they are more impaired than the average contact allergy patient. In a case-control study among Danish eczema patients, it was found that in the years after being

[24] (Johansen, et al., 2015)

diagnosed, significantly more fragrance positive female patients reported to have eczema present (almost) all the time compared to patients suffering from other contact allergies[25]. In the years after being diagnosed, impaired quality of life (QoL) has also been demonstrated in fragrance positive female patients. Using the disease-specific questionnaire Fragrance Quality of Life Index (FQLI), fragrance positive female patients reported significantly worse scores for the following questions compared to female eczema patients with other contact allergies: "You must take special measures in your daily life to avoid situations that could provoke your rash", "You restrict physical contact with your family/friends in order to avoid provoking your rash", "You are often worried about being exposed to things that can provoke your rash", and "You miss being able to smell nice"[26]. Before being diagnosed, eczema patients with fragrance allergy are equally impaired in their overall QoL as other eczema patients. However even before receiving their diagnosis of fragrance allergy, female eczema patients have significantly worse scores on the questions: "You must take special measures in your daily life to avoid situations that could provoke your rash", and "You miss being able to smell nice".

This evidence clearly suggests that when using WTP results from contact allergy, we are applying a "conservative" (on the low side) assessment of the welfare loss for fragrance allergy.

Review of WTP literature

A thorough literature study over estimates for willingness to pay for avoiding (or accepting) the risk of fragrance allergy and other skin diseases has been conducted.

Estimates of WTP for avoiding fragrance allergy has not been found. Instead, relevant literature on willingness to pay in relation to other skin disease has been identified and reviewed. The identified literature covers diseases such as contact allergy, atopic dermatitis and psoriasis; including the following list considered as key references:

- (Beikert, et al., 2014)
- (ECHA , 2016)
- (Bickers, et al., 2006)
- (Lundberg, Johannesson, Sliverdahl, Hermansson, & Lindberg, 1999)
- (Parks, Balkrishnan, Hamel-Gariepy, & Feldman, 2003)

In Beikert et al. (2014), estimates of WTP for atopic dermatitis (AD) were found. Patients were asked to name an absolute sum they were willing to spend per month for a complete cure of their disease. 35.7 % of the AD patients would

[25] Heisterberg M V, Menné T, Johansen JD. Fragrance allergy and quality of life - development and validation of a disease-specific quality of life instrument. *Contact Dermatitis* 2013; **70**:69–80.

[26] Heisterberg M V, Menné T, Johansen JD. Fragrance allergy and quality of life - a case-control study. *Contact Dermatitis* 2014; **70**:81–9.

accept to spend up to €50, 23.6 % would accept up to €100, 25 % would spend up to €300 and 6.8 % would spend more than €300[27].

We have used the average of the three lowest ranges and a minimum of the high range (€25, €75, €100 and €300) to compute a weighed monthly average WTP of around €97. This corresponds to an annual value of €1,164 in 2016-prices, which converted to DKK and corrected for purchasing power parities corresponds to approx. DKK 12,060 in 2018-prices.

One of the other key references is a Swedish study by Lundberg et al. (1999). They have conducted a willingness to pay study among 366 patients with psoriasis and atopic eczema aged 17 to 73 years, attending the dermatology outpatient clinic in Sweden. The respondents were asked using contingent valuation and bidding game approach to state their willingness to pay for cure of their disease. The study found a mean WTP of around SEK 1,000 per month for atopic dermatitis estimated on replies from 132 AD patients[28]. This indicates a relatively high annual willingness-to-pay as it amounts to about 8% of the respondent's monthly income. When correcting the value for purchasing power parities and forecasting to 2018-prices, the WTP would be approximately 13,600 DKK per person per year[29].

(ECHA , 2016)[30] includes a description and discussion of WTP assessment of the mild and severe dermatitis in four EU countries. The report is based on a study that ECHA commissioned to develop WTP estimates[31] and it compares the results of the specific study with a review of available literature. The ECHA WTP study covered the use of two valuation approaches and performed a number of statistical tests on the results. The study covered the following EU Member States: the Czech Republic, Italy, the Netherlands and the UK. In total around 3,600 respondents completed the questionnaires so while response rates varied between 10% and 60%, overall the study includes a large sample.

The results of the study are presented below.

[27] 9% would not consider a monthly investment in the cure of their skin disease

[28] (Lundberg, Johannesson, Sliverdahl, Hermansson, & Lindberg, 1999)

[29] Based on an exchange rate 0.8 SEK per DKK of and inflation of 36% from 1999 to 2018

[30] (ECHA , 2016)

[31] (Maca, 2014)

Picture 2-1 Willingness-to-pay values for skin irritation, source: (ECHA , 2016)

Table 1: Willingness-to-pay values for skin irritation (scaled to EU28)

Health endpoint	C_{2012}
Mild, acute dermatitis	227
2x/year	289
4x/year	329
1x/year for 2 years	308
1x/year for 5 years	352
1x/year for 10 years	339
2x/year for 2 years	271
2x/year for 5 years	391
2x/year for 10 years	447
4x/year for 2 years	334
4x/year for 5 years	383
4x/year for 10 years	615
Severe, chronic dermatitis	1,055

Source: Maca et al. (2014)

The (ECHA , 2016) is a review of the main study and includes further comparison of the result with the literature. It concludes that for mild acute dermatitis, the value of €227 per case seems appropriate. But for the servery chronic dermatitis, the value of €1055 per case seems much too low. The review recommends using a value around €1800 per year in that case. That is equivalent to around 13,800 DKK per year in 2018 prices.

(Bickers, et al., 2006) has estimated the different cost components of various skin diseases for US. The intangible effects have been included - though the specific approach to the assessment is not described in detail. The estimated cost per person is presented below.

Table 2-19 Intangible costs skin diseases in USA 2004

	Prevalence million people	Annual intangible costs in $ million	Costs per person in $ per year
Psoriasis	3.1	2,300	742
Atopic dermatitis	15.2	2,600	171
Contact dermatitis	72.3	1,900	26

Source: (Bickers, et al., 2006)

The costs have been estimated based on indexes for the effects on quality of life and WTP values for a few skin diseases taken from Lundberg et al. 1999 and Parks et al. 2003. In that sense, the study does not present its own WTP results.

Parks et al. 2003 has reviewed existing and therefore older studies on WTP for various diseases. The review includes for example Lundberg et al. 1999 so there is to some degree an overlap and references to the same basic studies. The value of atopic dermatitis is based on Lundberg et al. 1999.

Willingness to pay based on number of symptom days with restricted activity

An alternative way to estimate the willingness to pay includes two elements. Firstly, one has to estimate number of days where the symptoms have effect on the activity that a diagnosed person can and will do. Secondly, the value of one such day with some form of restricted activity is estimated.

In the current study, the number of days with restricted activity meaning the diagnosed person cannot work but also will have to restrain from social activities amounts to 5.6 days per year as an average for all that have been diagnosed with fragrance allergy, see Table 2-16.

Reviewing the available literature on WTP values for symptom and restricted activity days reveal that there are no newer studies than those used in Sørensen et. al. (2004). From that study, a relevant value for the WTP of avoiding one day with restricted activity is around 427 DKK in 2002 price level. It means around 550 DKK in 2018 price level[32].

Using the value of 550 DKK per day, a WTP can be estimated by 5.6 times 550 DKK equal to 3,080 DKK per person per year. However, using this approach would also imply that non-diagnosed persons would have a WTP of avoiding the sick days of 2.1 times 550 DKK equal to 1,050 DKK per person per year. It should be noted that we have assumed no intangible costs for those not being diagnosed in the current study. This is potentially an underestimation of the true intangible costs and it is further discussed below when concluding on the WTP.

It should also be noted that diagnosed persons might have days with symptoms, but where the severity of the symptoms does not prevent them from working. In (Sørensen, Gudum, & Serup-Hansen, 2004) the assessment of the intangible costs in relation to contact allergy was based on a WTP estimate for such "symptom days" and an expected average number of "symptom days". The unit value for a "symptom day" was 100 DKK and it was assumed that contact allergy results in symptom days for 20% of the year, i.e. about 73 days. The resulting estimate of the intangible costs for contact allergy was DKK 7,315 in 2002 prices (approx. DKK 9,360 in 2018-prices). The same study assumed that patients were only absent from work 1.6 days per year.

WTP based on quality of life indexes

Another approach to estimate the willingness to pay is using DALYs (Disability adjusted life year) and monetisation of the DALYs. DALY can be thought of as one lost year of 'healthy life', and the burden of disease can be thought of as a measurement of the gap between current health status and an ideal situation where everyone lives into old age, free of disease and disability.

DALYs were developed to reflect the sum of years of life lost (YLL) due to premature mortality and years lived in disability/disease (YLD). YLDs represent

[32] Inflation from 2002 to 2018 around 28% (Danmarks Statistik, 2019)

the number of disease/disability cases in a period multiplied by the average duration of disease/disability and weighted by a disease/disability factor.

DALYs take into account the number of years living in a less than perfect health state, and are calculated as follows: $DALY = YLD$, where YLD stands for Years Lived with Disability, is calculated as follows:

$$YLD = Number\ of\ cases * Average\ disease\ duration * Disability\ weight$$

To obtain the value of a DALY, the Value of a Statistical Life must be divided by the number of DALYs corresponding to a premature death. This number varies and is a function of the age at which death occurs, which itself depends on the nature of the risk considered (here, chemical exposure health impacts).

From the brief review conducted, there are several valuations for DALYs presented in the literature. For example, Stassen et al. (2007)[33] estimate that the cost of a DALY for severe morbidity health effects is €87,000. According to a website about persistent organic pollutants[34], the value of a DALY in the US is calculated as $120,000 as of 2008. This is equivalent to approximately €76,500 (using 2008 exchange rates). This calculation is based on dividing the Value of a Statistical Life (VSL) by the number of DALYs corresponding to a premature death. A study by Highfill and Bernstein (2014)[35] values a DALY averted as the value of a year of life in full health and sets this as being in the range of $100,000 to $200,000. This is equivalent to a range between €63,500 and €127,000. However, the study recommends the use of the lower estimate.

We will use the lower estimated the value of one DALY at €63,000. The table below includes values for the disability weight related to diseases closes to fragrance allergy. It is atopic dermatitis and contact allergy. The disability weights are here drawn from the GBD 2018[36].

[33] Stassen et al. (2015); DALYs versus WTP for Environmental Health Priority Setting based on Data of Air Pollution and Noise in Flanders. Available at: https://lirias.kuleuven.be/handle/123456789/407179

[34] http://www.popstoolkit.com/economic/training/overview/benefit+quantification/daly.aspx

[35] Highfill and Bernstein (2014): Using Disability Adjusted Life Years to Value the Treatment of Thirty Chronic Conditions in the U.S. from 1987-2010. Available at: https://www.bea.gov/papers/pdf/highfill_bernstein_2014_dalysall.pdf

[36] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Disability Weights. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018.

Table 2-20 Disability weights for skin diseases

Type of disease	Disfigurement level	Symptoms	Disability weight[37]
Severe atopic dermatitis	Disfigurement, level 3, with itch/pain	has an obvious physical deformity that is very painful and itchy. The physical deformity makes others uncomfortable, which causes the person to avoid social contact, feel worried, sleep poorly, and think about suicide.	0.576 (0.401–0.731)
Mild contact dermatitis	Disfigurement, level 1 with itch/pain	has a slight, visible physical deformity that is sometimes sore or itchy. Others notice the deformity, which causes some worry and discomfort.	0.027 (0.015–0.042)
Moderate contact dermatitis	Disfigurement, level 2, with itch/pain	has a visible physical deformity that is sore and itchy. Other people stare and comment, which causes the person to worry. The person has trouble sleeping and concentrating.	0.188 (0.125–0.267)
Mild atopic dermatitis	Disfigurement, level 1 with itch/pain	has a slight, visible physical deformity that is sometimes sore or itchy. Others notice the deformity, which causes some worry and discomfort.	0.027 (0.015–0.042)
Moderate atopic dermatitis	Disfigurement, level 2, with itch/pain	has a visible physical deformity that is sore and itchy. Other people stare and comment, which causes the person to worry. The person has trouble sleeping and concentrating.	0.188 (0.125–0.267)

Source: GBD 2017 sequelae, health states, health state lay descriptions, and disability weights

Based on these data, the WTP can be estimated as illustrated below.

Table 2-21 Estimated WTP based on disability weights

	Disability weight	Estimated WTP
Mild atopic dermatitis/ Mild contact dermatitis	0.027 (0.015–0.042)	12,600 DKK per year
Moderate atopic dermatitis/ moderate contact dermatitis	0.188 (0.125–0.267)	88,000 DKK per year
Severe atopic dermatitis	0.576 (0.401–0.731)	270,000 DKK per year

[37] Confidence interval in brackets

Using this approach, the WTP values are significantly higher than the results of the other approaches. This has been noted in the literature and the main reason is that the values of one DALY are based on the WTP for mortality effects.

Conclusion on WTP

The results of having assessed the different literature and approaches to estimate a relevant WTP for avoiding the negative impact on quality of life from having fragrance allergy are summarised in Table 2-22.

For the literature, we have identified WTPs that cover skin diseases such as atopic dermatitis and contact dermatitis. The WTP values converge around a level of 12.000 to 14.000 DKK per year. While these estimates are based on solid methods it should be noted that they rely on few primary studies.

Using instead the WTP based on the number of sick-day yield annual intangible cost for non-diagnosed at 1,050 DDKK per year and 3,080 DKK per year for diagnosed. WTP based on the DALY approach brings potentially very high estimates. However, the DALY based values for mild skin disease imply same values as for the literature review of related skin diseases.

Table 2-22 Summary WTP-estimates per approach[38]

Approach	WTP in DKK per person per year	Comment
WTP for atopic dermatitis and contact dermatitis	1,500 - 13,800	The low value is not really an estimate of WTP. The main primary studies suggest between 12,000 and 13,800 DKK.
WTP based on number of sick days and value of a restricted activity day	3,080	Significantly lower values per person, however the estimates only cover the willingness to pay for the actual sick days
WTP based on DALY approach	12,000 - 270,000	Potential very high values owing to DALYs being based on WTP for mortality effects

Based on the above different data and considering the pros and cons of the different approaches, we use the estimates for related skin diseases as our primary WTP estimate. Therefore, the best estimate of the WTP is around the order of 13,800 DKK per person per year.

Before concluding on estimation of the intangible costs, it should be discussed whether there is overlap with the WTP and the private medical expenditures.

For WTP estimates for atopic dermatitis and contact dermatitis identified in the literature, it is not clear whether the private costs are included in the underlying

[38] The WTPs are for a person that have been diagnosed

assessment and the derived estimates. It is therefore not known how large these private medical costs might be for the persons that have stated their willingness to pay. However, from the design of the WTP studies it is most likely that the private expenditure has been included by those stating the WTP. Hence, we assume that, the estimates include private expenditures for similar lotions, creams and other kinds of medicine.

Medical expenses of a symptom day as defined in Sørensen et. al. (2004) are likely to be rather limited, and here it would seem most reasonable to conclude that there is no double counting of costs, when using a *WTP based on number of sick days*. These values are however only related to the most severe symptom days, where the fragrance allergist would have to take sick-leave.

When taking into account that the WTP for might include private costs of treatment, we estimate the intangible costs to be 9,700 DKK per year. This is calculated by subtracting the private expenditure of around 4,100 DKK per year from the best estimate of the WTP at 13,800 DKK.

A range to be used for the sensitivity analysis in Section 3.4 is estimated using the values from 3,000 to 13,800 DKK per person per year. It could be argued that an even higher value based on DALY's could be considered in the sensitivity analysis. But we have conservatively refrained from this.

2.6 General assumptions

Table 2-23 shows the general assumption used in the analysis, such as the social discount rate, the base year for the analysis, exchange rate and assessment period. The framework and methodology applied in the study is generally based on the Danish guidance paper in socio-economic assessments (Finansministeriet, 2017).

In Denmark, a taxation factor (Nettoafgiftsfaktor) of 1.325 is used in socio-economic analysis to account for the difference in prices paid by private citizens and paid by public authorities. All prices paid by private citizens include product taxes and VAT, while public institutions are exempt from VAT and some other taxes. In order to ensure that the socio-economic assessment is based on goods and services that are all valued at market prices, the taxation factor is applied to prices that do not include VAT and other taxes.

Another correction factor that should be applied is the Marginal Cost of Public Funds. This factor accounts for the fact that public funds based on tax revenue is estimated to have a negative impact on the national economy. However, the effect of adjusting prices and accounting for the marginal cost of public funds is relatively minor as only a small part of the overall loss is accrued by public authorities.

Table 2-23: DK assumptions

	Unit	Value	Source
Social Discount Rate, Year 0-35	Rate	4 %	(Finansministeriet, 2017)
Social Discount Rate, Year, 36+	Rate	3 %	(Finansministeriet, 2017)
Purchasing power parities (PPPs) 2016 Denmark	PPP (EU28=1)	10.4225	(Eurostat, 2019)
Taxation factor	Factor	1.325	(Finansministeriet, 2017)
Marginal Cost of Public Funds	Factor	1.1	(Finansministeriet, 2017)
Base year	Year	2018	Assumption
Assessment period	Years	50	Assumption

3 Results

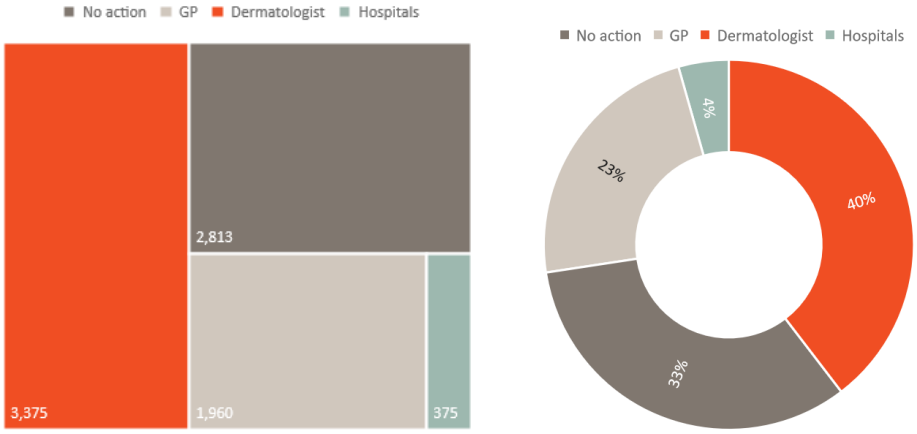
3.1 Diagnosis and course of treatment

As described in Chapter 2, the estimated annual number of new cases with fragrance allergy in Denmark are approx. 8,500 people. This number includes people who have been diagnosed with fragrance allergy by a dermatologist or through clinical investigations. In addition, it also includes people living with fragrance allergy without taking action and people who have consulted their general practitioner but are symptom treated and not referred to a dermatologist. We have - as described in Chapter 2 - defined four typical endpoints for new cases of fragrance allergy:

- Endpoint 1: Sensitized population living with symptoms (no action)
- Endpoint 2: Sensitized population going to GP (GP)
- Endpoint 3: Sensitized population referred to dermatologist through GP (Dermatologist)
- Endpoint 4: Sensitized population referred to hospital through GP/dermatologist (Hospital)

Figure 3-1 shows the annual number of cases with fragrance allergy divided on endpoint. The figure shows that the two main groups are people taking no action (33%) and people who are diagnosed by a dermatologist (40%).

Figure 3-1 New annual cases with fragrance allergy



As discussed on Chapter 1 and 2, we are using the assessment of the number of new annual cases of fragrance allergy to estimate the development of the population of adults with a fragrance allergy diagnose over time. We assume that the annual number of new cases and the division among diagnosis endpoints are constant over our assessment period of 50 year; see Figure 3-2.

Figure 3-2: Annual number of new cases and division in diagnosis endpoints

After being diagnosed with fragrance allergy, the individuals will start their daily treatment of the disease and have annual consultations with their dermatologist. The degree of daily treatments and number of consultations depends on severity of the individual case.

Figure 3-3 shows how many of those diagnosed in 2018 that continue to experience symptoms and therefore receive treatment. The assumed decrease in symptoms over time lead to a gradual reduction in the number of patients for the remaining lifetime of the 2018 cohort. The average age when diagnosed is, as described above, 49 years and the remaining lifetime is assumed at 33 years. Hence, this cohort is assumed to have remaining lifetime including year 2051.

Figure 3-3: Output 2: Annual number of treated, single cohort

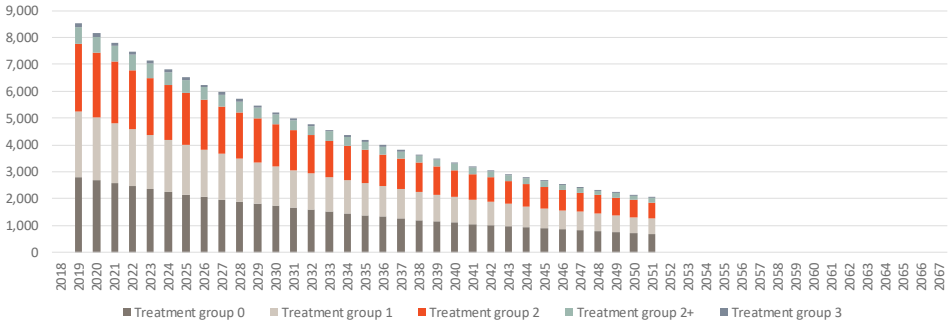


Figure 3-4 show the annual number of treated patients, when looking at people diagnosed in 2018 and forward.

Figure 3-4: Output 3: Annual number of treated, (patients diagnosed in 2018 and beyond)

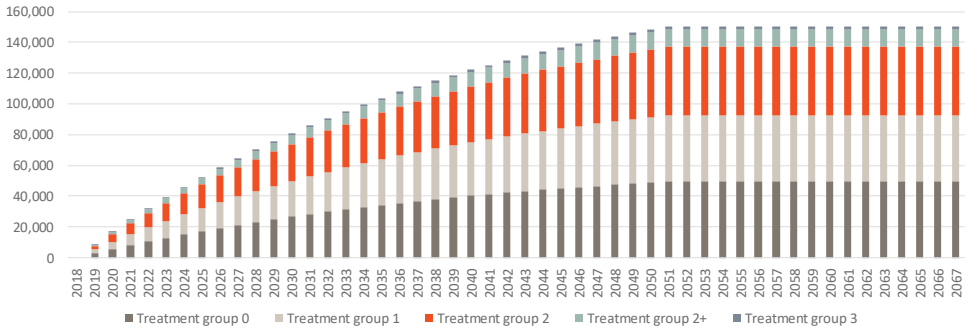
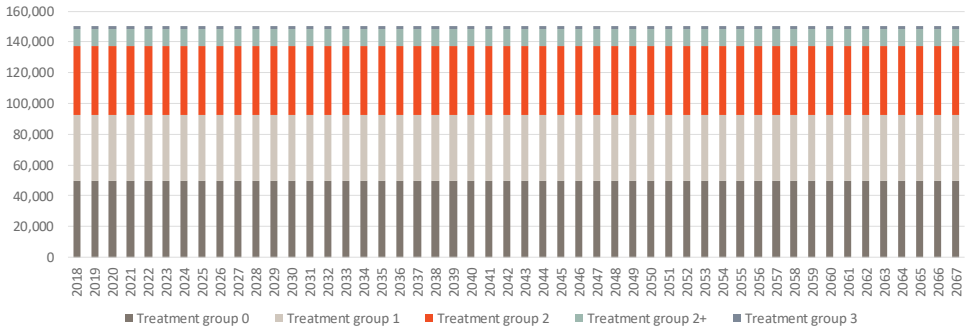


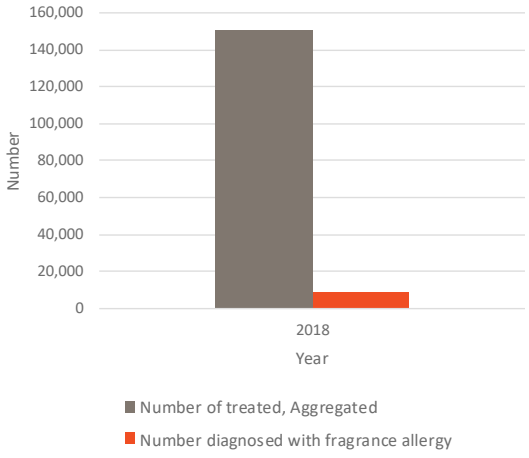
Figure 3-5 shows the constant annual number of treated patients from 2018 and until 2047, when taking the current burden of disease into account (i.e. people diagnosed before 2018).

Figure 3-5: Output 4: Annual number of treated, CBD



Finally, Output 5 is covering all patients that receive diagnose and treatment in one year. The numbers are for one year, so opposite to the previous outputs, it does not include a 50-year assessment period.

Figure 3-6: Output 5: Number of treated (diagnosed in the past) and new cases being diagnosed in one year



3.2 Socio-economic cost of fragrance allergy in Denmark

The socio-economic consequences of getting fragrance allergy for an average case is estimated at approx. DKK 182,000 (Output 1)[39]. This value is the discounted sum of all the cost elements over the lifetime of the average case.

The estimated direct health care costs covered by the public health care system comprise only about 3% of the total costs. The private costs related to creams and other medicine comprise about 28% of discounted costs. The indirect costs of loss productivity accounts for 26% of the total discounted costs, while the intangible costs comprise the remaining 43%. This detailed distribution by cost elements for an average patient with fragrance allergy (Output 1) is presented in Table 3-1.

The estimated total discounted costs for an average case of fragrance allergy may seem rather high. It should be noted that the cost of the disease for a single individual is calculated for the remaining lifetime. As discussed in Chapter 2, the average age at the time of diagnose is assessed to be 49 years and the average remaining lifetime is 33 years. It has also been discussed in Chapter 2, that although the disease is chronic, there is evidence indicating that over time the share of patients with symptoms will decrease (Bregnbak, Thyssen, Zachariae, & Johansen, 2014). Table 3-1 presents the costs for a case the person has symptoms over all of the remaining lifetime. The annual reduction in patients experiencing less symptoms is applied only for outputs 2 to 4.

Table 3-1: Socio-economic costs expressed in monetary unit (discounted as NPV and undiscounted) and share in % for an average patient with fragrance allergy diagnosed in 2018 (Output 1). DKK in 2018-prices.

	NPV (DKK)	Share (%)	UNDISCOUNTED (DKK)
Direct cost			
Cost of diagnosis	1,800	1%	1,800
Costs of daily treatment (public)[1]	4,400	2%	7,400
Private expenses	50,000	28%	90,900
Total direct costs	*56,300*	*31%*	*100,200*
Indirect cost			
Production loss	47,300	26%	70,800
Marginal Cost of Public Funds	600	0%	900
Total indirect cost	*47,900*	*26%*	*71,700*
Intangible cost			
Quality of life detriment	77,500	43%	140,800
Total intangible cost	*77,500*	*43%*	*140,800*
Total costs	**181,700**	**100%**	**312,800**

[39] The individual has fragrance allergy during the entire remaining lifetime.

Note 1: Public cost of daily treatment includes both subsidies to private expenses and annual consultations to medical professionals.

The above table refers to output type 1 (an average patient). Our model estimates nearly the same distribution of the different cost elements for the other three types of outputs.

For all cases diagnosed with fragrance allergy in 2018 the socio-economic costs amount to approx. DKK 1.0 billion (Output 2). The costs for people getting the disease from 2018 and forward are interesting since these costs can be influenced by policies that would reduce the number of new cases (Output 3). This burden of disease amounts to the significant costs of around DKK 20 billion over a 50-year assessment period[40]. Another interesting result is the consequences when looking at all people either in treatment or being diagnosed with fragrance allergy now and in the coming 50 years (Output 4). This amounts to a cost of approx. DKK 34 billion. Finally, the annual costs (Output 5) express how much fragrance allergy costs society per year. The annual costs are estimated at 1.5 billion DKK.

Table 3-2: NPV of fragrance allergy in 2018 (DKK), 50-year assessment period

	Measurement	NPV, 2018 (Million DKK in 2018 prices)
Output 1: Average case	An average patient diagnosed in 2018[1]	0.18
Output 2: Single cohort	Patients diagnosed in 2018	1,000
Output 3: All new cases	Patients diagnosed in 2018 and forward	20,700
Output 4: Total of existing and new cases	Patients diagnosed in 1985 and forward[2]	34,100
Output 5 Annual costs	All patients diagnosed in 2018 and before - costs for one year	1,500

Note 1: The individual has fragrance allergy during the entire remaining lifetime. The cost is estimated for an average case, and the cost presented here will therefore differ from individuals having light or severe fragrance allergy.
Note 2: 24 % of the diagnosed population in 1985 is included in the number of treated in 2018.

3.3 Extrapolation to EU

The assessment of the costs of fragrance allergy for the Danish society has been done using the best available data. Some of the data include EU wide studies and other data and assessments are based on Danish conditions. Given that the main input on prevalence and incidence are drawn from European studies, we consider it feasible to extrapolate the results to an EU28 estimate.

[40] Net present value over the 50-year period using 4% and 3% discount rates as indicated in Table 2-23

The extrapolation to EU28 is based on the following assumptions:

- Using the prevalence data indicating that the share of the sensitized population in EU is between 4% and 6%, we present costs in range that reflects this variation in the assessed prevalence of fragrance allergy in EU.
- The number of new cases is extrapolated by population size in Denmark relative to EU28
- The distribution of cases by endpoint and treatment group is assessed and assumed to be the same and
- The costs of diagnosing and treatment are adjusted to EU price level and converted from DKK to EUR.

The Danish population account for approx. 1.1 % of the EU28 population in 2018 (Eurostat, 2019). The EU estimate assumes an upscaling of the 1,1% for DK to 100% for EU28. As mentioned, the data on the prevalence of fragrance allergy in the general population are based on different studies including studies of the situation in EU. Hence, there are factors indicating that the share of the population being diagnosed would not vary significantly across EU.

The costs difference between Denmark and average EU for the unit of costs of each element - costs of visit to GP or to a dermatologist is estimated by adjusting the cost level with a Purchasing Power Parities (PPP) conversion rate. The cost and price level in Denmark are relatively high - approximately 30% higher than the EU average. The average EU28 costs are therefore reduced by 30% compared to the estimate for Denmark.[41]

Table 3-3 presents the economic cost of fragrance allergy in EU28 using this extrapolation method.

[41] The current exchange rate is DKK 7,46 to EUR 1 (Danmark Nationalbank, 2019) and with costs difference about 30%, the PPP conversion of the values in DKK is done dividing by a factor DKK 9,75 (Denmark) to 1 EUR (EU28) for Health to account for different price-levels (Eurostat, 2019).

Table 3-3: NPV of fragrance allergy for EU28 in 2018 (EUR), 50-year assessment period

	Measurement	NPV EU28 in 2018 (Million EUR in 2018-prices)
Output 1	Costs of one case diagnosed in 2018	0.019
Output 2: Single cohort	Patients diagnosed in 2018	7,300 - 10,900
Output 3: Annual	Patients diagnosed in 2018 and forward	150,800- 226,200
Output 4: Total	Patients diagnosed in 1985 and forward	248,200 - 372,300
Output 5: Annual costs	All patients diagnosed in 2018 and before - costs for one year	11,000 - 16,400

It cannot be ruled out that there could be national differences in the specific diagnose and treatment process between countries. However, given that the direct public health care costs comprise a relatively small share of the total costs, differences in e.g. visits to specialist or hospitals will not affect the overall assessment in any significant way. It can be noted that Denmark had the seventh highest health spending per capita and the fifth highest health spending as % of GDP in EU28 in 2017 (OECD, 2019). Given that price and cost levels are generally higher in Denmark than in EU28, this suggests that by accounting for cost and price level differences, the main differences will be accounted for.

3.4 Sensitivity analysis

The socio-economic cost calculations are sensitive to changes in key parameters. The sensitivity assessment consider firstly the sensitivity of the assessment of the costs of one fragrance allergy case and then the sensitivity of the aggregated population assessments.

For the costs of one case of fragrance allergy, the primary cost drivers relate to the *length of treatment period*, the *level of annual expenses* such as direct expenses to daily treatment, quality of life detriment and production loss. It is relevant to consider the sensitivity to each of these parameters.

It has been assessed that the average age when being diagnosed is around 49 years of age. If the average age would be for example 10 years younger, then the remaining lifetime would be 43 years instead of now 33. Given that the costs of the additional years will be discounted, the additional costs for 10 more years would be relatively small. Similarly, if the average age is higher for those being diagnosed. Hence, we apply a conservative approach.

Regarding the three cost components, they all accounts for a substantial share of the costs of one case.

The direct health care costs include the costs for the public health care system and the private expenses on medicine. The public health care costs comprise a relatively small share and the total cost of one case is not sensitive to this component. For the private costs, the estimated costs are sensitive to the specific use of moisturisers and creams. This component comprises 27% and it means that if the use is 50% lower, then the total costs will be reduced by 14%.

For the indirect costs, the productivity loss, the number of days off work could be higher or lower than the estimated 5.6 days. One day more or less would change the total cost of one fragrancy allergy case by 5%.

For the intangible costs, the estimated WTP is subject to uncertainty. Section 2.5.1 includes the discussion of WTPs and how to estimate the intangible costs. A range for the intangible costs of 3,000 DKK to 13,800 DKK per person per year is applied in the sensitivity assessment.

Regarding the number of fragrancy allergy cases, the number of patients diagnosed at dermatologist per annum is estimated at 3,750. It is our base estimate for the population projection, and a higher (lower) number will result in a higher (lower) overall number of diagnosed and treated in all scenarios. The effect of changing the number is a more or less proportional change in the total estimated costs.

The following parameters have been included in a quantitative sensitivity assessment:

- The number of patients diagnosed at dermatologist per annum. It is our base estimate for the population projection, and a higher (lower) number will result in a higher (lower) overall number of diagnosed and treated in all scenarios.
- The number of patients undergoing treatment is reduced each year due to a fraction of patients experiencing a reduction in their symptoms
- WTP estimates for fragrance allergy

Table 3-4 show the applied ranges for the sensitivity analysis.

Table 3-4: Input values for sensitivity analysis

	Unit	Basis	Low	High
Patients diagnosed at dermatologist	Number of Patients	3,750	2,813 (75% of basis)	4,688 (125% of basis)
Annual decrease in number of patients in treatment due to a reduction in their symptoms	%	4.4	3.4	5.4
WTP estimate	DKK	9,700	3,700	13,800

Additionally, the sensitivity of the assumptions on annual visits to the dermatologist has been assessed. The sensitivity analysis assumes that after the diagnose has been given, no further visits are assumed in the following years. This is a very conservative assumption, as some visits will take place in particular for those with more severe symptoms.

Using these ranges, the results of the sensitivity analysis are shown in Table 3-5. The sensitivity analysis shows that both the level of quality of life detriment and the number of people living with fragrance allergy has a relatively large effect on the results. The assumptions on the annual number of visits to the dermatologist during the lifelong treatment period have limited effect on the estimated social costs.

Table 3-5 Sensitivity analysis - NPV of fragrance allergy for DK in 2018, million DKK

	Output 1	Output 2	Output 3	Output 4
Basis	**0.18**	**1,000**	**20,700**	**34,100**
Patients diagnosed at dermatologist, Low	0.18	756	15,670	25,862
Patients diagnosed at dermatologist - High	0.18	1,260	26,117	43,103
Decrease in number of treated - 3.4%	0.18	1,104	22,725	38,811
Decrease in number of treated - 5.4%	0.18	925	19,299	30,844
No visits to the dermatologists after diagnosing	0.18	983	20,370	33,580
WTP estimate - Low	0.14	756	15,720	25,533
WTP estimate - High	0.22	1,180	24,430	40,598

3.5 Comparison with literature

We have not identified studies that have estimated the socio-economic costs of fragrance allergy. It is therefore difficult to compare the estimated total costs in the current study with values found in the literature.

For the assessment of the intangible costs, we have assessed the literature and compared different studies. Our willingness to pay estimate for avoiding the negative welfare effects of fragrance allergy is based on the results of this literature review. Hence, for the intangible costs, our results are comparable with the results found in the literature as discussed above in Section 2.5.1.

For the direct and indirect costs, there is a German study where the direct and indirect costs per person with atopic dermatitis per year has been estimated (Augustin, 2001). The results are presented in the below table.

Table 3-6 Costs for skin diseases in Germany 2001

	Costs per year in DM (in 2001)	In DKK 2018[42]
Direct public health care costs	2064	10,500
Direct private health care costs	1396	6,980
Total direct costs	3396	17,480
Indirect costs (production loss)	662	3,370
Total costs	4059	20,850

Source: (Augustin, 2001)

The direct costs are higher than what we have estimated as the direct costs. We have estimated the annual direct costs at 3,000 DKK per person and indirect costs of 2500 DKK.

Another study that included direct and indirect costs is Bikers et al. 2004. They have estimated the total costs for different skin disease based on prevalence data and the direct and indirect (productivity loss) costs. For the most comparable diseases, the costs are presented below.

Table 3-7 Costs for skin diseases in USA 2004

	Prevalence million people	Total direct and indirect costs in $ million	Costs per person in $ per year
Psoriasis	3.1	1358	438
Atopic dermatitis	15.2	1628	107
Contact dermatitis	72.3	2191	30

Source: Bikers et al. 2004

Contact dermatitis is the diagnose being closest to fragrance allergy and converting the 2004 USD values to DKK 2018 price level leads to an annual costs per patient of 220 DKK. This is a very low figure and very low compared to all the other studies.

We have estimated direct costs of at average of around 3,000 DKK per person per year. While this shows a difference, it is difficult to compare, as the US study does not indicate specifically what has been included. Also, the distribution of patients with various severity degree could significantly change the estimation.

The study (Sørensen, Gudum, & Serup-Hansen, 2004) has estimated the total costs of on case of contact allergy using an approach similar to what been used for the present study. They arrived at costs of one case of contact allergy at

[42] Currency exchange rate in 1991 was 3.8 DKK per DEM and inflation has been 34% from 1999 to 2018

290,000 DKK in 2003 prices. This would be equal to approximately 350,000 DKK per case in 2018 prices.

Overall, few studies can be used for comparison. Of the few found examples, the German study indicate higher direct and indirect costs though not significantly different, while the US study suggests lower costs. The Danish study on the costs of diagnoses that could be caused by exposure to hazardous chemicals estimated higher costs per case contact allergy. Therefore, it seems that the present study provides the right order of magnitude estimates of the costs of fragrance allergy.

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