REVIEW OF THE SCIENTIFIC EVIDENCE OF AIR POLLUTION CAUSING HEALTH EFFECTS IN PEOPLE LIVING IN THE VICINITY OF CONCENTRATED ANIMAL FEEDING OPERATIONS (CAFOs)

Gennemgang af de eksisterende videnskabelige undersøgelser af helbredseffekter af luftforurening hos naboer til store husdyrbrug

Scientific Report from DCE – Danish Centre for Environment and Energy No. 401 2020

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Abstract:	This report reviews the literature concerning health effects of exposure to emissions from animal husbandry and health effects in people living in the vicinity of concentrated animal feeding operations. This review has shown, that there is a scarcity of studies shedding light on the association between health and neighborhood exposure to farming operations. There are a few studies on short-term effects in farming exposed susceptible groups. These studies add to the knowledge on the acute effects of the farm related exposures, but they need to be followed up by cohort studies in or-der to estimate the long-term effects of the exposures emitted from the farming operations
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Contents

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1 Words

ATS ; American Thoracic Society
CAFOs ; Concentrated animal feeding operations
CFUs ; Colony-forming units
COPD ; Chronic Obstructive Pulmonary Disease
CS ; Cross sectional study
Endotoxin ; Lipoprotein from the cell wall of Gram-negative bacteria. (10 EU is approximately 1 ng endotoxin)
ERS ; European Respiratory Society
FEV_1 ; Forced expiratory volume in 1st second
FU ; Follow up study (Cohort)
FVC ; Forced vital capacity
GIS ; Geographic information system
GP ; General Practitioner
IR ; Incidence Rate
LF ; Lung function
LUR ; Land Use Regression
MMEF; Maximal Mid Expiratory Flow: is the peak of expiratory flow as taken from the flow-volume curve in liters per second at 50% of FVC.
MRSA ; Methicillin-resistant staphylococcus aureus
NCDs ; non communicable diseases
NH_3 ; Ammonia
NiLS ; Niedersächsischen Lungenstudie:
Lung Health Study in Lower Saxony
NSBH testing; Nonspecific bronchial hyper-responsiveness testing
NSBP ; Nonspecific bronchial provocation
OR ; Odds Ratio
PM ; Particulate matter
PM_{10} ; Particulate matter <10µm
$PM_{2.5}$; Particulate matter <2.5µm
PR ; Prevalence rate;
SES ; Socioeconomic status
SF12 ; Short Form Survey (SF-12):
Self-reported outcome measure assessing the impact of health on an individual's everyday life. It is often used as a quality of life measure.
Tiffeneau index ; (FEV_1 / VC)
VAS ; Visual Analog Scale
VC ; Vital capacity
VGO ; Veehouderij en gezondheid omwonenden:
Animal husbandry and health in neighbors

2 The task from Ministry of Environment of Denmark

A thorough literature review is requested to examine all known studies relating to the health of neighbors related to air pollution from livestock farming. Dutch descriptions of the problem indicate that it is still unknown what type of air pollution causes the observed health problems. Several exposures are being studied such as ammonia, dust and endotoxins, as well as a combined exposure effect as possible causes of health problems or aggravation. The review should therefore broadly cover health effects caused by air pollution related to livestock farming.

It is expected that all Danish literature, as well as foreign literature, especially European and North American literature on the topic is relevant to or comparable to Danish production conditions, and therefore will be included and assessed in the review. A literature review is requested to clarify:

- What symptoms have been observed in neighbors to livestock farming related to air pollution?
- Do the scientific articles indicate a link between symptoms and certain substances in air pollution from livestock farming e.g. dust, endotoxins or ammonia?
- Has causality been documented between certain substances in the air from nearby livestock farms and the observed symptoms?
- Is there any indication of how problems detected can be dealt with by exposure threshold limits, legislation concerning distance to exposure or other precautions?
- Are there indications of other factors affecting the health of neighbors of livestock farming?

3 Dansk resumé

3.1 Opgaven

Der ønskes udarbejdet et grundigt litteraturstudie, der gennemgår alle kendte undersøgelser, der vedrører sundhedsforhold for naboer relateret til luftforurening fra husdyrbrug.

I hollandske beskrivelser af problemstillingen fremgår det, at det endnu er uvist, hvilken type luftforurening der forårsager de observerede problemer. Der arbejdes både med ammoniak, støv og endotoksiner, samt evt. en kombineret effekt af disse eksponeringer som mulige årsager.

Undersøgelsen skal derfor forholde sig bredt til helbredseffekter forårsaget af luftforurening relateret til husdyrbrug. Det forventes, at al dansk, samt udenlandsk litteratur, særligt europæisk og nordamerikansk litteratur, der har relevans for eller kan sammenlignes med danske produktionsforhold, indgår i og bliver vurderet i undersøgelsen.

Der ønskes foretaget en litteraturgennemgang, der afklarer:

- Hvilke symptomer er der observeret hos naboer relateret til luftforurening fra husdyrbrug?
- Er der i de videnskabelige artikler indikeret en sammenhæng imellem symptomer og bestemte stoffer i luftforurening fra husdyrbrug fx støv, endotoksiner eller ammoniak?
- Er der dokumenteret kausalitet imellem de konstaterede symptomer og bestemte stoffer i luftforureningen fra nærliggende husdyrbrug?
- Er der anvisninger på, hvorledes evt. konstaterede sundhedsproblemer kan håndteres ved grænseværdier, afstandsregler eller andre forholdsregler?
- Er der indikationer af andre forhold, der har betydning for sundhed for naboer til husdyrbrug?

3.2 Resumé

Danmark er ét af de steder i verden med den højeste tæthed af dyr sammenholdt med landets størrelse. De 13,3 mio. svin, 23 mio. fjerkræ, 1,49 mio. kvæg og 2,5 mio. pelsdyr, overvejende i store landbrugsfaciliteter, medfører høje landbrugsrelaterede udslip af partikler og gasser. Dette resulterer i stigende sundhedsproblemer i den del af befolkningen, der bor tæt på gårdene.

Landbrugsmiljøet som erhvervsmæssig eksponering er grundigt undersøgt, mens sundhedseffekter blandt beboere tæt på de store husdyrbrug ikke er undersøgt i samme grad. Landmændene er mere udsatte end resten af befolkningen, men til gengæld kan beboere i de omkringliggende områder være mere følsomme over for virkningerne af eksponeringerne. Små børn, ældre og mennesker med kroniske sygdomme er generelt mere sårbare over for miljøforurening.

Landbrugsfaciliteter udgør en trussel for miljøet og for menneskers sundhed på flere måder: Først og fremmest pga. den intensive produktion med et højt forbrug af handelsgødning og/eller husdyrgødning som resulterer i et kvælstofoverskud, der kan udvaskes til grundvandet. I Danmark har et højere indtag af nitrat i drikkevandet vist sig at være forbundet med øget risiko for kræft i tyk- og endetarm (Schullehner et al., 2018).

For det andet spredes emissioner i form af partikler, gasser (fx ammoniak), bakterier, endotoksiner, vira og skimmelsvamp fra husdyrbruget, hvilket således medfører luftforurening i de omkringliggende områder. De vigtigste kilder til partikler frigivet fra gårdene omfatter pollen og andre allergener direkte fra husdyrene eller fra halm og strøelse anvendt på gårdene. Partikler frigivet fra landbrugsdrift kan også omfatte patogene mikroorganismer og resistente bakterier. Infektioner i befolkningen forårsaget af andre zoonotiske patogener, er desuden set fx i Holland, hvor Q-feber forårsaget af *Coxiella burnetii* var forbundet med en høj tæthed af gedebrug i området (Smit et al., 2012). Aktuelt har undersøgelser af spredning af CoVid-19 vist, at mink er kilde til CoVid transfektion mellem dyr og mennesker. Det har vist sig, at CoVid-19 virus inficerer dyr, der igen inficerer personer i det omgivende samfund. Samtidig opstår der ændringer i genomet under passagen gennem dyrene tilbage til befolkningen, (SSI-Denmark 2020) (https://www.ssi.dk/aktuelt/nyheder/2020/smitte-hos-mink-og-mennesker)

For det tredje bidrager sekundære uorganiske aerosoler, herunder ammoniumsulfat og ammoniumnitrat, væsentligt til fine partikler i miljøet pga. ammoniaks reaktioner med sure gasser og partikler i atmosfæren. Hovedparten af ammoniakemissionerne i Danmark stammer fra landbrugsaktiviteter (>90%), og inden for landbrugssektoren kan ca. halvdelen af emissionen tilskrives håndtering af gødning (særligt i stalden) (Nielsen et al., 2018). Landbruget forårsager en betydelig luftforurening sammenlignet med andre menneskeskabte kilder. Dette medfører eksponering af befolkningen og efterfølgende sundhedseffekter (Brunekreef et al., 2015; Lelieveld et al., 2015). I Danmark har nitrat i luftforurening vist sig at være forbundet med børns astma (Holst et al., 2018; Holst et al., 2020) og $PM_{2,5}$ forureningen relateret til dyreproduktion er forbundet med øget dødelighed i mange vestlige lande (Lelieveld et al., 2015). Miljømæssige påvirkninger fra dyreproduktion er dog stadig ikke undersøgt i større omfang, hverken for de nærliggende omgivelser eller som en del af den generelle luftforurening.

Forskellen i gødningsbrug mellem DK og NL hidrører hovedsageligt fra den mængde husdyrgødning, der føres ud på markerne. I DK sikrer den såkaldte harmonilovgivning en lokal fordeling af husdyrgødning. Dette er reguleret anderledes i NL, hvor en stor del af gødningen fra husdyrbrug eksporteres til Tyskland Belgien og Frankrig. N- og P-ratioen for gødning er højere i NL fx i år 2010, hvor det kan aflæses af figur 4.1, at for P, var forskellen omtrent 15 mod 40 kg-P/ha i henholdsvis DK og NL; for N var ratioen 125 mod 200 kg-N/ha i DK og NL (Willems et al., 2016). Dette fører generelt til mere lokal eksponering for NH_3 i løbet af gødningssæsonen i NL, men med lokale forskelle afhængigt af gødningsbehandlingsteknologier og lokal gødningsfordeling via biogasanlæg. I DK er fx forsuring som gødningsbehandlingsteknologi mere udbredt end i NL.

Ifølge en af de inkluderede undersøgelser, har man i Holland etableret en vejledende grænse for naboers udsættelse for en komponent af bioaerosolen, endotoksin, som emitteres fra landbrug. For endotoksin er der fastsat en vejledende grænse for udsættelse af naboer til dyrehold på 30 EU (Endotoxin Unit)/m^3 (Farokhi, Heederik, and Smit 2018).

Ud fra Eurostat kan man se, at det samlede antal dyreenheder i NL næsten er dobbelt så stort som i Danmark.

Der er et større antal km^2 agerjord brugt til at distribuere gødning fra dyrene på i DK. NL eksporterer imidlertid flydende gødning til Belgien, Frankrig og Tyskland, hvilket kan mindske eksponeringen for landbrugsemissioner og mindske forskellen til det danske niveau med hensyn til gylle deponeret pr. areal, se tabel 5.2.

Ser man på befolkningstætheden i de to lande er der en klar forskel med ca. tre gange flere personer pr km^2 i NL. Det betyder, at flere mennesker udsættes for landbrugsemissioner i NL sammenlignet med DK.

Dette udelukker ikke lokale forskelle betinget af enkelt store intensive husdyrbrug – på engelsk "Concentrated Animal Feeding Operations" (CAFOs) i de to lande. Da gårdenes størrelse i Danmark gennemsnitlig er større en de hollandske, vil sådanne problemstillinger derfor sandsynligvis oftere forekomme i Danmark end i Holland.

Denne rapport fokuserer på potentielle helbredsrelaterede effekter hos beboere med bopæl tæt på husdyrhold forårsaget af udsættelse for gasser (fx. ammoniak), bakterier, allergener (bioaerosoler) og partikler, der stammer fra landbrugsdriften. Denne rapport har derimod ikke til formål at behandle nitratforurening af drikkevand, generel luftforurening forårsaget af landbruget, zoonotiske infektioner (smitte mellem dyr og mennesker) eller spredning af antimikrobiel resistens i samfundet.

3.3 Partikler, aerosoler og gasser fra dyrehold

En række forskellige komponenter udsendes fra drift af stalde. De består af partikler og gasser. Partiklerne er en speciel blanding bestående af foder, fækale partikler, hår, hudpartikler, mikroorganismer, vira, allergener osv.

Emissionen af disse meget forskellige komponenter gør, at de forurenende stoffer, der kommer fra landbrug, er meget forskellige fra andre kilder til luftforurening fx fra trafik. Luftforureningskomponenterne på gasfase fra landbrug består af ammoniak (NH_3), hydrogensulfid (H_2S) og kuldioxid (CO_2). Ud over disse gasser og partikler udsendes en række lugtstoffer, der består af komponenter med delvis eller lav flygtighed, som stammer fra nedbrydningen af biomasse på gårdene og gødning fra dyrene. Emissioner af forureningskomponenter finder også sted under udbringning af gødning fra gødningslageret til markerne. Dette forekommer specielt i slutningen af vinteren og foråret.

Ammoniak udledt fra landbruget reagerer kemisk med sure gasser og partikler i atmosfæren, og bidrager dermed til produktionen af sekundære uorganiske partikler, der blandt andet indeholder ammonium (NH_4^+). Disse sekundære partikler udgør en del af $PM_{2,5}$-koncentrationen i luft. Således bidrager landbrug til helbredseffekter ved at bidrage til den generelle $PM_{2,5}$-forurening, et faktum som ofte ignoreres eller glemmes.

De meteorologiske forhold, herunder især vindretning, vindhastighed og temperatur, har betydning for spredning og omdannelse af partikler og gasser, og dermed for hvor stor eksponering naboerne til en given gård udsættes for.

Ofte er denne eksponering ikke synlig eller erkendt af de mennesker, som udsættes for forureningen. Imidlertid er lugtstofferne (forbindelserne med delvis eller lav flygtighed), der udsendes fra gårdens aktiviteter, let genkendelige for mennesker, og de bliver derfor bemærket af beboerne i områderne omkring gårdene.

Koncentrationerne af partikler, toksiner og gasser i miljøet omkring gårdene er meget lavere end det, som landmændene udsættes for i deres arbejde med husdyrene i staldene. Det er stadig ikke fuldt belyst, om disse koncentrationer er tilstrækkelige til at fremkalde sygdom og sundhedseffekter hos den befolkningsgruppe, der bor i nærheden enten generelt eller i modtagelige dele af befolkningen.

3.3.1 Eksponeringsvurdering

For at bestemme befolkningens eksponering anvendes en række metoder, der spænder fra målinger af koncentrationer af forskellige komponenter såvel udenfor i nærmiljøet, som indenfor i produktionen, til egentlige eksponeringsmodeller som f.eks. regressionsmodeller baseret på arealanvendelse (Land Use Regression – LUR), avancerede fysisk-kemiske modeller og lokal skala spredningsmodellering. Denne type modeller er som regel ret avancerede, og de to sidstnævnte typer tager højde for kemisk omsætning i atmosfæren og meteorologiske parametres indvirkning på transport og spredning. I mange undersøgelser af eksponering anvendes enklere metoder, fx baseret på antallet af gårde i nærheden af den befolkningsgruppe som eksponeringen undersøges for og/eller afstanden til den nærmeste gård.

Den underliggende grundantagelse for denne form for eksponeringsestimering er, at de koncentrationer, der måles, modelleres eller estimeres lige uden for døren, er repræsentative for den personlige eksponering.

3.3.2 Eksponeringsniveau og eksponeringsegenskaber

En række undersøgelser har målt landbrugsrelaterede eksponeringer i nærheden af gårde. I USA fandt Thorne, Ansley, Perry et al. (2009) endotoksinniveauer mellem 26 og 29 EU/m^3 160 m i vindretningen fra svinestalde svarende til mindre end 1% af de gennemsnitlige koncentrationer inden for staldene, men med enkeltmålinger så høje som 140 EU/m^3 . I en tysk undersøgelse havde individer, der boede i landdistrikter med intens dyreproduktion, et øget niveau af endotoksin i deres baghave på omkring 2 EU/m^3 (Schulze et al., 2006). I en undersøgelse fra Texas, USA, konkluderede Gibbs et al. (2004), at der blev fundet bakterier og svampe fra svinestalden lige uden for stalden og længere væk i vindretningen. Bakterierne blev observeret i niveauer, der potentielt kunne medføre sundhedsfare . Dette fund blev understøttet af Green et al. (2006) i en anden amerikansk undersøgelse, der fandt en markant højere koncentration af bakterier inde i produktionsanlægget (18.132 CFU (colony forming units)/m^3 i gennemsnit) sammenlignet med koncentrationen udenfor målt på en position længere væk imod vindretningen (63 CFU/m^3 gennemsnit). Derudover faldt niveauet støt i vindretningen ud til ca. 150 m, hvor koncentrationen af bakterier var 10% af niveauet målt lige uden for stalden og på niveau med målingerne taget mod vindretningen. Guidry et al. (2017) målte koncentrationen af hydrogensulfid på tre skoler nær industrielle husdyrfaciliteter og konkluderede, at hydrogensulfidkoncentrationen steg med faldende afstand til husdyrbrug. Alt i alt understøtter eksisterende undersøgelser, at eksponeringsniveauerne tæt på husdyrbrug er væsentligt lavere end indenfor i selve produktionsanlægget, men stadig er langt fra ubetydelige.

En del studier bruger det samlede niveau af typen og antallet af landbrug i området som mål for eksponering. Dette kan fx være antallet af gårde i en radius af 500 m fra boligen. Et eksempel på dette er undersøgelsen udført af Kravchenko et al. (2018) af sammenhængen mellem dødelighed og CAFO-tæthed i North Carolina. Fordelen ved metoden er, at den er let at anvende. Ulempen er, at eksponeringsvurderingen er upræcis med risiko for fejlslutninger forårsaget af underliggende parametre, der ikke tages højde for på det individuelle niveau (såkaldte "økologiske fejlslutninger"). Disse undersøgelser er i bedste fald en indikation af en mulig sammenhæng, men bør efterfølges af studier af højere kvalitet med individuel eksponeringsinformation og information om potentielt konkurrerende variable.

3.3.3 Adressebaseret eksponeringsvurdering

Eksponeringsvurderingen kan baseres på afstanden til nærmeste gård med dyrehold kombineret med afstandsvægtede PM_{10}-emissioner fra dyreholdet. Dette kan også stratificeres for dyreart og afstand til nærmeste stald med en bestemt dyretype, fx geder eller svin.

Både individuelle eksponeringsproxyer (baseret på ovenstående) og relative eksponeringsproxyer benyttes i denne metode, fx ved sammenligning af to forskellige områder med hhv. høj og lav tæthed af dyrehold.

En del af de undersøgelser, der baserer sig på adresse og afstand, har ikke parametre relateret til spredning, afsætning eller kemisk omdannelse af luftbårne komponenter inkluderet i analysen (van Dijk et al., 2017). Emissionernes bidrag til eksponeringen estimeres i disse tilfælde udelukkende ud fra lineær fortynding baseret på den omvendte afstand mellem hjemmeadressen og kilden til emission.

Fordelen ved denne tilgang er, at det giver mulighed for at inkludere mere nøjagtige data for placering af forskellige dyretyper. Ulemperne er knyttet til det faktum, at fysiske og kemiske processer, der er vigtige for emission, transport, omdannelse, spredning og afsætning af luftforureningskomponenter fra dyrehold, ikke tages i betragtning, ligesom den faktiske kemiske sammensætning af komponenter ikke adresseres.

3.3.4 Regressionsmodeller baseret på arealanvendelse (LUR)

En anden måde at udføre beregning af eksponering på er ved anvendelse af regressionsmodeller baseret på arealanvendelsesdata, såkaldte LUR-modeller (Land Use Regression). LUR-modeller er baseret på en kombination af målinger af luftforureningskomponenter og estimering af emissioner af PM og andre forbindelser, fx ammonium eller endotoksiner baseret på produktionen, (de Rooij et al., 2017). Eksponeringen er baseret på en række lokale parametre som fx: i) antal dyr inden for bufferzoner på f.eks. 500 eller 100 m omkring adressen, ii) afstand (og omvendt afstand vægtet med antal dyr på nærmeste gård) til nærmeste dyrebrug og dyretype, iii) middelværdier af en eller flere meteorologisk parametre som fx temperatur, lufttryk, vindhastighed, relativ fugtighed, varighed af nedbørsepisoder, mængde af nedbør, solskinstimer og vindretning. Målestationer der ligger i nærheden af de gårde med dyrehold, der studeres, samt eventuelle "baggrundsstationer" (målestationer der ligger så langt fra lokale kilder, at kilderne ikke har indflydelse på koncentrationerne) kan også inkluderes. I studiet af de Rooij et al. (2017) var den målestation, der blev anvendt som baggrundsstation, dog ikke lokaliseret længere væk end 500 m fra det nærmeste dyrehold.

Fordelene ved LUR-tilgangen er, at det er muligt at anvende en række detaljerede data om fx forskellige dyretyper, og hvor de er placeret i området. Desuden tages meteorologiske variationer i begrænset omfang i betragtning ved hjælp af denne tilgang.

En ulempe ved fremgangsmåden er, at LUR-modeller ikke er baseret på kausal modellering, men i stedet tager udgangspunkt i mønstergenkendelse. Det kan give ret nøjagtige resultater fx i reproduktionen af mønstre med høje og lave koncentrationer, men det giver ingen muligheder for at forstå, hvorfor koncentrationerne er høje eller lave. Midlingsperioden er vigtig i forhold til karakterisering af variationerne i fx koncentrationerne af PM_{10}. Hvis midlingsperioden er for lang, bliver det vanskeligt at adskille baggrundsniveauet fra det lokale signal. Desuden skal baggrundsstationen befinde sig opstrøms og højst sandsynligt mere end 500 m væk fra det studerede område for ikke at være påvirket af lokale kilder. I undersøgelsen foretaget af de Rooij et al. (2017) er gennemsnitsperioden ret lang (en uge), og placeringen, der anvendes til baggrundsmålinger, ligger sandsynligvis for tæt på de andre dyrehold til at give den nødvendige information om baggrundsniveauer.

3.3.5 Deterministisk modellering

Endelig kan eksponeringsvurdering beregnes ved hjælp af kausale, deterministiske modeller, der beskriver atmosfærisk transport, spredning, kemisk transformation og eventuelt afsætning. Sådanne modeller er typisk Gaussiske røgfanemodeller, som drives af detaljerede meteorologiske datasæt og inkorporerer data om emissioner fra punktkilder (fx afkast på staldbygninger, markstakke og gødnings-/gyllebeholdere) og arealkilder (fx udbringning af husdyrgødning og afgrøder på marker). Disse modeller baserer den luftbårne spredning på beskrivelsen af de styrende fysiske processer, herunder transport, spredning og afsætning og på den relevante teori (om fx grænselagshøjde og opblanding) og tager derudover andre relevante parametre i betragtning, fx data om arealanvendelse i forbindelse med beregning af turbulens og afsætning.

I en undersøgelse foretaget af Boers et al. (2016) udføres eksponeringsvurderingen for lugt på basis af beregninger med den lokale spredningsmodel "STACKS" (Hollands pendant til den danske OML-model). Resultaterne er angivet for 98 percentilen af timeværdier for lugtkoncentration svarende til den metode, som de hollandske myndigheder anvender i forhold til lugt.

I en anden undersøgelse foretaget af Blanes-Vidal et al. (2014) blev der beregnet en samlet adressebaseret eksponering for koncentrationer af ammoniak fra de væsentligste kilder inden for et udpeget undersøgelsesområde ved hjælp af en kombination af en atmosfærisk langtransportmodel, der beregnede baggrundskoncentrationsniveauet, og en lokalskala transport- og afsætningsmodel (OML-DEP), som beregnede den lokale koncentrationsfordeling på et 400 m x 400 m grid. OML-DEP modellen beregnede også den kemiske omsætning af ammoniak til ammonium (på partikelform). Undersøgelsen udført af Blanes-

Vidal et al. (2014) antog, at de beregnede ammoniakkoncentrationer kan anvendes som en proxy for den luftbårne eksponering for lugt, og med udgangspunkt i modelresultaterne blev hustandskoncentrationerne beregnet ved hjælp af invers afstandsvægtet multivariat interpolation.

Fordelene ved deterministisk modellering er, at den giver en dybere forståelse af kausalitet og af de processer, der påvirker luftforureningskomponenterne hele vejen fra udsendelse til eksponering.

Ulemper ved denne metode kan være, at det undertiden er vanskeligt at skaffe alle relevante inputdata til modellen. Det kan fx være vanskeligt at skaffe data, der beskriver arealkilde-emissioner (Boers et al., 2016), og uden dem vil en del af bidraget til eksponeringen mangle, da arealkilde-emissioner kan yde et væsentligt (kortvarigt) bidrag, når gødning / gylle køres ud på markerne.

3.4 Resumé af de vigtigste fund

3.4.1 Lugt

Studierne af lugt viste samstemmende, at der er flere symptomer i befolkningen med stigende lugtkoncentration. Det ses, at lugtgenerne er højere ved svinebedrifter sammenlignet med kvæg og andre bedrifter. NiLS-studiet fra Niedersachsen i Tyskland fandt en dosis-respons sammenhæng mellem lugt og dårligere fysisk og følelsesmæssigt velbefindende. Det samme blev set i et hollandsk studie i et område med høj tæthed af husdyrbrug. Korrigeret for andre betydende faktorer viste analysen, at lugtirritation var forbundet med gener for den generelle sundhed som luftvejs- og mave-tarm symptomer (Hooiveld et al., 2015). Endnu et studie viste, at lugtgener var relateret til selvrapporteret lugt fra husdyrbrug og lugtgener fra gyllespredning (Boers et al., 2016). Alle disse studier er tværsnitsstudier, og der er derfor risiko for påvirkning af resultaterne fra andre forhold end selve lugten. Det er vanskeligt at undersøge effekten af en eksponering, der ikke er skjult for de udsatte grupper. Når eksponeringen samtidig virker frastødende på mange, vil der kunne opstå en øget opmærksomhed på egne symptomer, som fører til en overrapportering af gener. Ud fra disse studier kan det på baggrund af de tilgængelige studier uddrages, at lugt fra landbrug er en kilde til irritation / ubehag for personer i nærområdet. Det er imidlertid vanskeligt at fortolke sammenhængen mellem lugtstyrke og helbredsklager. En dansk mediationsanalyse af Blanes-Vidal (2014a, b) undersøger sammenhængen mellem eksponering for ammoniak og symptomer direkte [*eksponering* → *symptomer*] såvel som indirekte via lugtgener [*eksponering* → *lugtgener* → *symptomer*]. Mediationsanalysen peger på mulige direkte luftvejseffekter af ammoniak. Forfatterne angiver, at disse virkninger kan forklares ved, at ammoniak enten er markør for generel udsættelse for organiske stoffer fra landbruget, fx endotoksin, eller at der er tale om en effekt af omvendt årsagssammenhæng, dvs. *eksponering* → *symptomer* → *irritation*.

3.4.2 Luftvejssygdom, symptomer og biomarkører

Resultaterne fra de forskellige undersøgelser er ikke umiddelbart sammenlignelige. Studierne af bedst kvalitet ser ud til at vise, at der en beskyttende virkning af at bo i nærheden af landbrug. Dette gælder især for allergisk astma i den befolkning, som bor i områder med intensivt landbrug.

VGO-projektet fra Holland (Borlée 2017) viste en omvendt sammenhæng mellem indikatorer for husdyrbrug og selvrapporteret astma samt Kronisk Obstruktiv Lungelidelse (KOL). Dette indikerer en beskyttende effekt af at bo i et område med landbrug for KOL. En anden undersøgelse fra den samme gruppe viste ligeledes en beskyttende sammenhæng mellem luftvejsinfektioner, luftvejssymptomer, astma, KOL og høfeber og en række indikatorer for landbrugseksponering. Undersøgelserne er alle tværsnitsstuder og mangler objektive målinger af sundhedsresultaterne, hvorfor det er svært at drage sikre konklusioner. Det er derfor ikke klart ud fra disse undersøgelser, hvordan luftvejssymptomer og sygdomme er relateret til landbrugseksponering, og forklaringen skal måske findes i socioøkonomiske forhold.

Tre undersøgelser skiller sig ud, fordi de er udført i områder uden en forudgående diskussion af landbrugsområdernes negative effekter. Disse er fra Holland (Hooiveld et al., 2016) og Wisconsin USA (Schultz et al., 2019). Den hollandske undersøgelse af befolkningens henvendelser til praktiserende læger for luftvejssygdomme viser beskyttende virkninger af at bo i et landbrugsintensivt område. Derimod viser undersøgelsen fra Wisconsin, USA, at luftvejsklager er hyppigere i områder med mange malkebesætninger i forhold til områder uden høj intensitet af landbrug. Risikoen for nyopstået astma steg, og risikoen for astmaanfald blev næsten fordoblet (1,8 til 1,9 gange) blandt de, der boede 1-3 miles væk fra en større bedrift (CAFO) sammenlignet med mennesker, der boede fem miles eller mere fra en CAFO. Endelig viste en undersøgelse fra Holland, der benyttede modelleret endotoksin-eksponering (de Rooij et al., 2019), en statistisk sikker stigning i hyppigheden af astma relateret til endotoksin-eksponeringen. Imidlertid faldt astmaforekomsten med faldende afstand til nærmeste gård, og det samme blev set for KOL. Dette understreger vigtigheden af bedre målinger af personlig eksponering og socioøkonomiske forhold snarere end blot afstanden til nærmeste gård.

I undersøgelser af generel sygelighed og dødelighed er der fundet modstridende resultater. I North Carolina, hvor befolkningen overvejende er udsat for svin, fandt man øget sygelighed og dødelighed i områder med høj landbrugsintensitet end i andre områder (counties) uden landbrugsaktivitet (Kravchenko et al., 2018). I modsætning til dette viser en hollandsk undersøgelse lavere sygelighed for en række sundhedsparametre i områder med intensivt landbrug sammenlignet med ikke-landbrugsområder (van Dijk, Smit, et al., 2016).

I panelundersøgelser af modtagelige grupper ses ingen sammenhæng mellem ammoniakeksponering og luftvejssymptomer hverken hos astmatiske børn (Loftus, Yost, Sampson, Torres, et al., 2015) eller hos KOL-patienterne (van Kersen et al., 2020). Imidlertid ses en tydelig effekt af partikeleksponering (ugemiddel af $PM_{2,5}$) blandt de astmatiske børn (Loftus, Yost, Sampson, Arias, et al., 2015).

3.4.3 Luftvejsinfektioner

En interessant observation i et studie fra Holland er en stigning i forekomsten af KOL med antallet af CAFO'er i eget postnummer (Hooiveld et al., 2016). Den øgede risiko for KOL stiger med alderen til hhv. 1,07 og 1,13 blandt henholdsvis 45+ årige og 60+ årige. Dette kan være en indikator for landbrugseksponeringens effekt på kroniske luftvejssygdomme. En undersøgelse af van Dijk (2016) viser en vigtig information, nemlig at den højeste udsættelse for fjerkræstalde øger risikoen for luftvejsinfektioner med en odds ratio på 1,17. Som opfølgning på denne undersøgelse brugte Smit et al. (2017) afstand til fjerkræbedrift som eksponering i forhold til indlæggelse for lungebetændelse. I studiet fandt de, at personer, der boede mindre end 1,15 kilometer fra den nærmeste hønsefarm, havde en øget risiko for lungebetændelse. De fandt samtidig, at den bakterie, der hyppigst blev fundet ved denne lungebetændelse, var *Streptococcus pneumoniae*.

De hollandske undersøgelser viser, at mennesker, der bor tættere på store gårde specielt med fjerkræ, har næste dobbelt så høj risiko for lungebetændelse, i sammenligning med mennesker, der bor længere væk. En metaanalyse af alle tilgængelige undersøgelser (Post et al., 2019) bekræfter risikoen for Q-feber i forbindelse med gedehold. Imidlertid blev den øgede risiko for lungebetændelse forbundet med fjerkræbedrifter ikke bekræftet i dette studie.

3.4.4 Allergi

Af tre studier på området er det kun ét studie af sammenhæng mellem allergi og husdyrhold, der identificerer faktorer, som er forbundet med lavere grad af atopi (allergisk sensibilisering). Dette studie, der er fra et område af Holland med høj intensitet af landbrug (VGO), viser, at endotoksineksponering er associeret til lavere forekomst af sensibilisering over for almindeligt forekommende allergener (de Rooij et al., 2019). Da undersøgelsernes design er ens, må forklaringen på forskellen i fund bero på forskellige metoder til at vurdere allergi og eksponering eller forskellige miljøer - VGO studiet er foretaget i et område med en blanding af forskellige landbrugstyper, hvorimod NiLS-studiet er fra Niedersachsen (Radon et al., 2007) er i et område domineret af svineproduktion, og landbruget i Wisconsin er domineret af malkebedrifter (Schultz et al., 2019). En anden væsentlig forskel kan findes i de øvrige variable, som forskerne har inkluderet i analyserne. Fx har Rooij et al. kontrolleret for opvækst i landbrug, en faktor som har vist sig at påvirke sensibiliseringshastigheden langt ind i voksenalderen (Elholm et al., 2018). Endvidere er det påvist, at landmænd og personer i landdistrikterne har lavere hyppighed af sensibilisering over for almindeligt forekommende allergener (Sigsgaard et al., 2020; Basinas et al., 2012; Elholm et al., 2016).

3.4.5 Lungefunktion

Ud fra de inkluderede studier ses en negativ sammenhæng mellem lungefunktion og udsættelsen for ammoniak og endotoksin. Sammenhængen mellem lungefunktion og partikeleksponering er marginal, og associationerne for partikler er svagere end for ammoniak. Dette indikerer tilsammen vigtigheden af landbrugsrelateret forurening ift. påvirkning af lungefunktion.

De hollandske studier viste, at FEV_1, FEV_1/FVC og maksimal midt-ekspiratorisk flow (MMEF) alle var signifikant lavere end forventet for beboere i de mest intensive landbrugsområder. I en analyse, hvor antallet af bedrifter blev brugt som proxy for eksponering, var MMEF sikkert lavere hos personer, der boede i et område med mere end 25 gårde inden for en radius på 1000 m fra bopælen (Borlée, Yzermans, Aalders et al., 2017). En senere analyse viser en sammenhæng mellem endotoksin-eksponering og luftvejssymptomer samt nedsat lungefunktion (de Rooij et al., 2019).

For panelundersøgelserne (Loftus, Yost, Sampson, Torres et al., 2015; Loftus, Yost, Sampson, Arias et al., 2015; van Kersen et al., 2020) ses en negativ effekt på lungefunktionen af ammoniak såvel som for partikeleksponering. Interessant for begge grupper synes IQR-effekten (dvs. forskellen i risiko for de 25% lavest og de 25% højest eksponerede) af partikler at være svagere end ammoniak IQR-effekten, hvilket indikerer vigtigheden af den landbrugsrelaterede ammoniakeksponering for lungefunktion. Dette i modsætning til at der ikke blev fundet nogen sammenhæng mellem ammoniakudsættelse og symptomer i de samme undersøgelser.

3.5 Konklusion

Denne gennemgang har vist, at kun få tilgængelige undersøgelser har kastet lys over sammenhængen mellem eksponering fra landbrugsdrift og sundhed blandt beboere i området. De inkluderede undersøgelser er overvejende tværsnitsstudier fra nogle få specifikke områder i den vestlige verden. Store landbrugsområder som det nordlige Spanien, det nordlige Italien og Polen forekommer ikke. Hvad angår undersøgelser af erhvervsmæssig eksponering blandt landmænd er litteraturen ligeledes domineret af tværsnitsstudier (Sigsgaard et al., 2020). Gårdmiljøet er grundigt undersøgt, og en række luftvejssygdomme forårsaget af det organiske støv på gårdene er beskrevet blandt landmænd og landarbejdere (Schenker et al., 1998; Sigsgaard et al., 2020).

Tværsnitsundersøgelser er et problem for risikovurdering, da årsagssammenhængen er vanskelig at vurdere i sådanne studier. Der er dog et par undersøgelser, som strækker sig over 3-9 måneder, af kortvarige effekter blandt astmabørn og KOL-patienter, som er udsat for landbrugseksponering. Undersøgelserne påviser akutte negative virkninger af landbrugseksponeringer på disse sårbare grupper. Men undersøgelserne bør følges op af andre studier, fx interventionsstudier, som kan vise en forbedring, hvis man fjerner eksponeringen eller kohortestudier for at estimere de langsigtede virkninger af eksponeringer fra landbrugsdriften. Fremtidige interventionsundersøgelser bør udføres som randomiserede kontrollerede forsøg og omfatte objektive mål for eksponering såvel som sundhedsresultater. Kohorteundersøgelserne bør også omfatte objektive mål for eksponering såvel som sundhedsresultater for at undgå bias på grund af den uundgåelige viden i befolkningen om potentiel eksponering, som kan føre til bias på grund af den lugt, de oplever. En interventionsundersøgelse af astmatiske børn fra det samme landbrugsområde i NW USA, som panelundersøgelserne opstod fra, er i gang og viser en signifikant reduktion i $PM_{2,5}$ i luften indendørs, når de blev udstyret med to luftrensere ”*HEPA-cleaners*”, i barnets soveværelse og i stuen. Luftrenserne havde ingen effekt på NH_3-koncentrationerne (Riederer et al., 2020; Masterson et al., 2020). I følge forskergruppen vil helbredsundersøgelsen blive publiceret i løbet af de kommende 6 måneder (Catherine Karr; personlig kommunikation).

Det har ikke været muligt at lave en egentlig risikovurdering på basis af de tilgængelige studier. Dette skyldes, at antallet af studier er lavt, og at langt de fleste studier er tværsnitsstudier, der ikke muliggør en sikker analyse af årsagssammenhængen.

På grund af heterogeniteten af de inkluderede studier har vi afstået fra at udføre en metaanalyse. Derfor har vi i det efterfølgende udført den bedst mulige syntese af evidens for at komme frem til nogle overordnede konklusioner.

3.5.1 Stærk evidens

Ifølge de foreliggende undersøgelser er der god dokumentation for, at ammoniakeksponering som en indikator for landbrugseksponering er forbundet med lugtgener hos den almindelige befolkning. En række undersøgelser har vist, at lugten fra landbrugsaktiviteter spredes til naboer, og irritationen øges med koncentrationen af eksponeringen på en dosisafhængig måde. I studierne er der benyttet antallet af gårde i omgivelserne (Radon et al., 2004; Hooiveld et. al., 2015), lugtestimering (Boers et al., 2016) eller modelleret ammoniak som en indikator for landbrugseksponering (Blanes -Vidal et al., 2014).

Undersøgelserne af Q-feber, en infektion med *Coxiella burnetii*, der kan overføres fra dyr til mennesker, benytter en række forskellige metoder, der alle påviser en øget risiko for Q-feber i forbindelse med gedeopdræt. Dette understøttes af en metaanalyse, der med stor sikkerhed finder en øget risiko for Q-feber i nærheden af store gedefarme (de Rooij et al., 2017; Post et al., 2019). Til trods for at alle undersøgelserne er fra Holland, anses evidensen for at være stærk.

3.5.2 Moderat til stærk evidens

Lungefunktion;; En veludført panelundersøgelse med astmatiske skolebørn i USA (Loftus et al., 2015a,b) viser en negativ effekt på lungefunktionen (daglig FEV_1) ved modelleret eksponering for $PM_{2,5}$ og NH_3 ved deres hjem- og skoleadresse. For en IQR-ændring (forskellen mellem de 25% laveste og 25% højeste) i $PM_{2,5}$ sås et fald i FEV_1 % på 0,9%, og yderligere et fald på 1,4%, når analysen blev begrænset til børn med atopi, som er sensibilisering over for almindeligt forekommende allergener. For sammenhængen mellem IQR ammoniakeksponering og lungefunktion fandt studiet en ændring i FEV_1% på 3,8%. I denne delundersøgelse blev der fundet et øget fald på FEV_1 på 6,3%, når analysen var begrænset til atopiske børn, der boede inden for en radius af 1,0 km fra en luftmoniteringsstation.

En panelundersøgelse af KOL-patienter identificeret via VGO-undersøgelsen fulgte patienternes daglige lungefunktion og symptomer morgen og aften i 3 måneder (van Kersen et al., 2020). Eksponeringen var de gennemsnitlige daglige niveauer af ammoniak og PM_{10}. Undersøgelsen viste, at en IQR-stigning i luftens indhold af ammoniak to dage før lungefunktions-målingerne om morgenen var relateret til en øget risiko for et fald i FEV1> 20% på 1,14 stigende til 1,23 med begrænsning af analysen til patienter med en strengere defineret KOL. Der blev fundet svagere, men signifikante virkninger for associeringen til PM_{10}-koncentrationen.

Interessant for både astma og KOL er, at IQR-effekten af $PM_{2,5}$ og PM_{10} på FEV_1 synes at være svagere end effekten af ammoniak. IQR gradienten indikerer vigtigheden af landbrugsrelateret eksponering for luftvejenes respons på den lokale luftforurening. Dette står i kontrast til resultaterne vedrørende symptomer i børneundersøgelsen, som er tættere forbundet med PM-effekten.

Ingen andre undersøgelser bekræfter resultaterne ovenfor, så beviset er stadig kun moderat til stærkt, da det skal bekræftes i andre veldesignede studier.

3.5.3 Moderat til svag evidens

Symptomer; Studier af skolebørn har vist stigende forekomst af luftvejssymptomer relateret til antallet af gårde i området (Mirabelli et al., 2006), men dette blev ikke fundet i NiLS-undersøgelsen ved brug af ammoniak som en indikator for landbrugseksponering (Radon et al., 2007).

For voksne er resultaterne blandede, og studierne er alle tværsnitsundersøgelser. Resultaterne spænder fra en vis effekt til en omvendt sammenhæng (en beskyttende virkning) af at bo tæt på gårde. Der kan dog findes eksempler på sammenhæng mellem landbrugseksponering og symptomer (Borlée et al., 2017). I denne undersøgelse fandt man flere luftvejssymptomer for KOL-patienter, der boede nær gårde. VGO-undersøgelsen viste en signifikant stigning i astmasymptomer forbundet med højere niveauer af endotoksin og med stigende PM_{10}-niveau estimeret med en Land Use Regression (LUR)-model der bygger på en statistisk sammenhæng mellem fx målte koncentrationer og diverse bedriftsparametre som fx antal husdyr, stalddimensioner etc. (de Rooij et al., 2019). Disse resultater peger på en potentiel rolle for udsendte bakteriekomponenter, såsom fx endotoksiner fra Gram-negative bakterier.

Lungefunktion; En kort opfølgning i NiLS-undersøgelsen viste, at udsættelse for høje ammoniakkoncentrationer (≥19.7 ug / m^3 ved hjemmet) var forbundet med et fald i FEV_1 (% forventet) -8,2 (-13.7.-2,7) men ingen effekt på FEV_1 / FVC (Borlée et al., 2017).

VGO-undersøgelsen viste, at FEV_1, FEV_1 / FVC og maksimal midt-ekspiratorisk flow (MMEF) alle var signifikant lavere end forudsagt hos de mennesker, der bor i det intensive landbrugsområde. Ved at bruge antallet af bedrifter i analysen var MMEF signifikant lavere hos personer, der boede med mere end 25 gårde indenfor en radius af 1000 m fra adressen.

I Wisconsin fandt Schultz et al. (2019) at lungefunktion (FEV_1) var lavere, hvis nærmeste CAFO var tæt på sammenlignet med lungefunktionen hos beboere, der boede længere væk i et eksponeringsrespons-lignende mønster. FEV_1% forventet var henholdsvis -8%, -12% og -13% ved at bo <1,6 km i forhold til hhv. <3,4 km, <4,8 km og <6,8 km fra nærmeste CAFO.

Alle disse undersøgelser er tværsnitsstudier, og derfor er beviset svagt og bør valideres i yderligere uafhængige undersøgelser. Der er således behov for flere undersøgelser med et stærkere design for at belyse disse sammenhænge tilstrækkeligt.

3.5.4 Svag evidens

Symptomer; Tværsnitstudierne giver blandede resultater for sammenhængen mellem symptomer og lugt. På grund af menneskets iboende evne til at lugte denne forurening, er det næsten umuligt at adskille virkningerne direkte relateret til lugt og de effekter, der medieres gennem irritation. En god dansk undersøgelse fandt ved hjælp af en mediationsanalyse en direkte effekt af ammoniak på luftvejssymptomer samt en indirekte effekt medieret via lugtgener (Blanes -Vidal et al., 2014). Imidlertid betragtes beviset som svagt, da dette er den eneste undersøgelse med denne type information.

Fra panelundersøgelser med sårbare personer ses ingen sammenhæng mellem ammoniakeksponering og luftvejssymptomer hverken hos de astmatiske børn (Loftus, Yost, Sampson, Torres, et al., 2015) eller hos KOL-patienterne (van Kersen et al., 2020). Imidlertid var $PM_{2,5}$ associeret til symptomer blandt astmabørnene (Loftus, Yost, Sampson, Arias, et al., 2015).

Den danske undersøgelse anvendte modelleret ammoniakeksponering på adresseniveau og psykosociale symptomer samt adfærdsmæssige ændringer. Undersøgelsen fandt i en mediationsanalyse en mulig direkte virkning af ammoniak på luftvejssymptomer. Forfatterne angiver, at disse virkninger kan forklares, enten fordi ammoniak er en markør for en generel udsættelse for organiske stoffer fra landbruget, fx endotoksin, eller det kan være en effekt af omvendt årsagssammenhæng, dvs. eksponering →symptomer →irritation.

Allergi; I undersøgelserne af allergi hos personer, der bor tæt på gårde, er det kun den nylige VGO-undersøgelse, der finder en effekt af landbrugseksponering for lavere forekomst af allergier. Imidlertid er dette set i andre undersøgelser, der indbefatter landmænd, andre der bor på landet, som ikke arbejder i landbruget, og er sandsynligvis en bekræftelse af en almindelig tendens for allergiforekomsten, der falder fra by til land til gårdmiljø.

Lungebetændelse; De observerede sammenhænge mellem fjerkræ i nabolaget og forekomsten af lungebetændelse har brug for mere opmærksomhed. Evidensen betragtes som svag ud fra nuværende undersøgelser.

Utilstrækkelig dokumentation

Effekten af CAFO'er på generel sygelighed og dødelighed er utilstrækkeligt undersøgt. De eksisterende undersøgelser mangler information om vigtige variable af betydning for sygdomsudviklingen, hvilket gør det svært at drage konklusioner ud fra de nuværende undersøgelser.

3.6 Afsluttende bemærkninger.

Alt i alt peger gennemgangen af de nuværende studier på luftvejsirritation i den almene befolkning på grund af landbrugseksponering i den omgivende luft på en dosisafhængig måde. Yderligere negative virkninger på helbredet findes i modtagelige grupper som astmatikere, især børn og KOL-patienter. Flere undersøgelser fra flere lande er nødvendige for at bekræfte resultaterne i de modtagelige grupper. Samtidig er der et tydeligt behov for opfølgningsundersøgelser af den generelle befolkning, som bor i nærheden af intensivt landbrug.

4 Intro

Denmark is one of the places worldwide with the highest density of animals compared to the size of the country. We have 13.3 mio pigs (pigs defined as ≥ 7.2 kg) predominantly in highly specialized farming facilities. On top of that, we have more than 23 mio broilers and laying hens, 1.49 mio cattle including 566,000 dairy cows and 2.5 mio mink and other fur production animals. These state of the art large farming facilities spread around the Danish country side give rise to high farming related emissions of particles and gasses, which in turn results in a rising health concern among the residents living close to the farms.

Although the farming environment as an occupational exposure has been thoroughly studied, not much has been done looking into the related community health affected by the large livestock operations close to residential areas. It has been a common understanding among farmers, that they are much exposed, much more than the rest of the population. This is still a correct interpretation, but residents in the surrounding areas may be more sensitive to the effects of the exposures such as young children, the elderly, and people with chronic non communicable diseases (NCDs). Groups who are in general more prone to effects of environmental pollution.

Farming operations are posing a threat to the environment and human health in three ways: Firstly due to the high manure "production" and build up. Manure is spread on the fields surrounding the farms and in case of surplus causing drinking water contamination, especially of the shallow ground-water magazines is one concern. In Denmark, nitrate pollution of the ground water resources has been shown to be associated to a higher risk of colorectal cancer in people with a higher intake of nitrate in drinking water (Schullehner et al., 2018).

Secondly local air pollution with emissions from the farms is causing exposure and unease in the populations in the surrounding area. Emissions from farms range from gasses like ammonia to bacteria, viruses and molds. These microorganisms can be found in the particulate air pollution surrounding the livestock operations (de Rooij et al., 2017). The main sources of particulate matter released from the farms contain pollen and other allergens directly from the farm animals or from straw and beddings used in the farms. Particulates released from farming operations may also include pathogen microorganisms like MRSA or other resistant bacteria in countries using antibiotics in the production of livestock. Other zoonotic pathogens causing infections in the populations like Q-fever caused by *Coxiella burnetii* has been found in the Netherlands in areas with a high density of goat farms (Smit et al., 2012). In this context, studies of spread of CoVid-19 has recently shown that mink is a reservoir and source of CoVid-19 transfection between humans and animals. At least in Denmark and in Netherlands it has been shown, that CoVid-19 virus is infecting animals and reinfecting people from the animal houses to the communities even with changes in the genome during the pass in man through animals back to the populations (SSI-Denmark 2020).

Thirdly on top of this, secondary inorganic aerosols including ammonium-sulfate and ammonium-nitrate is a major contributor to fine particulates in the environment caused by atmospheric irreversible reactions of ammonia with sulphuric acid and reversible reactions with nitric (and hydrochloric) acid.

The resulting products are particles containing ammonium, nitrate and sulfate. The majority of ammonia emissions arise from agricultural activities (>90%), and within the agricultural sector app. half of the emission can be ascribed to manure handling (especially in the barn) (Nielsen et al., 2018).

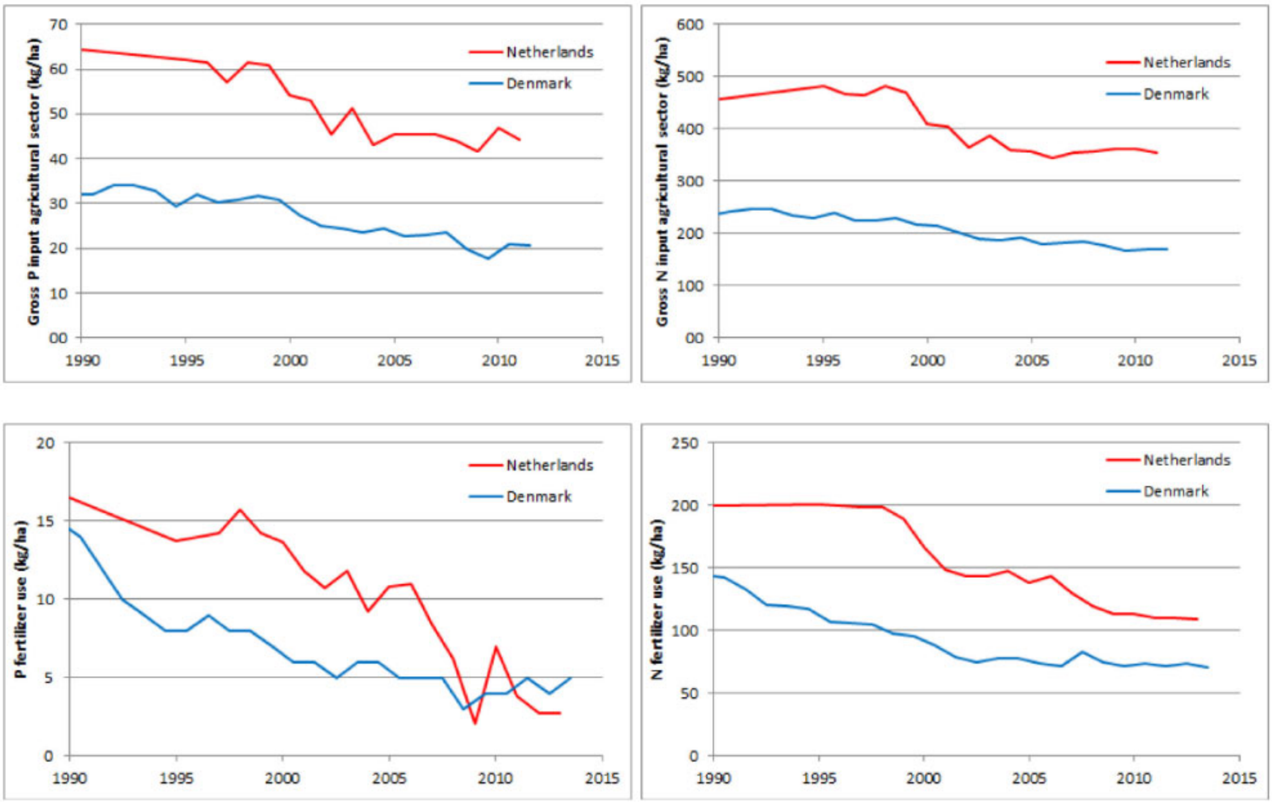

Figure 4.1. Trends of gross P and N input into agriculture, use of synthetic P and N fertilizer and the national P and surplus for the agricultural sector in Denmark and the Netherlands between 1990 and 2013 from (Willems et al., 2016).

The difference in fertilizer use between DK and NL relates mainly to the amount of livestock manure applied on the fields. In DK, the so-called manure harmony legislation ensure local distribution of livestock manure, while this is regulated differently in NL, where a large part of the manure from livestock farms is exported to Germany & France. Still the manure P- and N-rates are higher in NL, for e.g. 2010 it was for P roughly (by reading the figure 4.1) 15 vs 40 kg-P / ha in DK and NL, respectively; for N the numbers were 125 vs 200 kg-N / ha in DK and NL (Willems et al., 2016). This in general leads to more local exposure to NH_3 during the season for the application of manure in NL, but with local differences depending on manure treatment technologies (for instance more widespread acidification in Denmark), and local manure redistribution via biogas plants.

For the emission from farm houses, the picture is a bit different, as the general farm size in NL is smaller, the local emissions might be less intense, but more widespread. There is a higher population density in the areas in NL where the farms are located, and therefore more people are exposed to NH_3 and bioaerosols from production on an everyday basis.

This causes an exposure of the general population and subsequent health effects, which add a substantial proportion to the air pollution compared to other anthropogenic sources (Brunekreef et al., 2015; Lelieveld et al., 2015).

Nitrate in air pollution has been associated with children's asthma in Denmark (Holst et al., 2018; Holst et al., 2020), but it is also a part of the general air pollution, and as such it drives the total burden of diseases related to fine particulates in Denmark and Europe. Lelieveld et al., 2015 studied the global burden of PM air pollution on mortality and found that the PM 2.5 related to animal production was a major driver of mortality in many Western Countries (Lelieveld et al., 2015). However, the environmental effects of animal production is still an understudied area both in the nearby surroundings and as part of the general air pollution.

One of the reviewed studies, do mention a guideline value for endotoxin exposure of the neighboring population in the vicinity of farms to be promoted by the Dutch Health Council of 30 EU (Endotoxin Unit)/m^3 (Farokhi, Heederik, and Smit 2018).

This report will focus on the potential health effects on the nearby residents caused by exposures to gasses (i.e. ammonia), bacteria, allergens and particulate matter emitted from the farming operations. The current report is not meant to include nitrate or contamination of drinking water, general air pollution, zoonotic infections or spread of antimicrobial resistance in the community.

5 The CAFO-situation in Denmark and the Western World

In Denmark the concentration of animal feeding operations started in the 1980s with a gradual expansion of the individual farms and a reduction in the number of farms. At the same time the national production of animals per year increased. This intensification of the production led to an increase in the number of farmers suffering from respiratory diseases, described in the medical literature internationally (Donham et al., 1986; Haglind and Rylander 1987; Dosman et al., 1988; Rylander et al., 1989; Donham et al., 1989; Donham 1990; Donham et al., 1990; Cormier et al., 1991; Zhou et al., 1991; Malmberg and Larsson 1993; Zejda, Hurst, Barber, et al., 1993; Zejda, Hurst, Rhodes, et al., 1993; Larsson et al., 1994; Larsson, Malmberg, and Eklund 1994; Zejda et al., 1994; Quinn et al., 1995; Donham et al., 1995; Schwartz et al., 1995; Vogelzang et al., 1996) as well as nationally (Omland et al., 1999; Sigsgaard et al., 1997; Omland et al., 2000; Sigsgaard et al., 2000; Doekes et al., 2000; Iversen et al., 1988; Iversen et al., 1989; Iversen et al., 1990b, 1990a). This trend of increasing the farm size has continued into the present day (Basinas et al., 2012; Sigsgaard et al., 2020) leading in some instances, even in Europe, to the development of so called mega-farms or farm factories. This international trend of increased production is only made possible by import of cheap protein feeds enabling the farmers to feed more animals than what would be possible with the crops from their own fields, thus setting the farming operations free from the constrain of the area on fodder production (Robinson 2011). In Denmark the ability to grown the farm productions exponentially has been partly stifled by linking of the farm area (size) to the number of animal units at a farm, in order to be able to dispose of the manure buildup (the byproduct of meat production).

5.1.1 Complaints from the rural communities

Concurrent to this development there has been a rising awareness of odour among the residents living near animal farms or in areas with a high concentration of pigs or cattle. In particular this happened in the traditional farming areas in Europe DK, D, NL, I and E (Möhle 1998; Schiffman 1998; Radon et al., 2004; Radon et al., 2007; Schlaud et al., 1998; Schulze et al., 2011) and in North America, North Carolina, Iowa USA and Sascatchewan Canada (Schiffman 1998; Donham 2000; Kirkhorn 2002; Nimmermark 2004; Heederik et al., 2007; Dosman et al. 1988; Zhou et al., 1991; Zejda, Hurst, Barber, et al., 1993). In Denmark the first complaints over CAFOs from neighboring communities dates back to the early 2000s.

In 2002 Kirkhorn wrote about the American experiences with CAFOs in a preamble for a review: *"High-density concentrated animal feeding operations (CAFOs) have become an increasing source of concern with respect to their impact on health, the environment, and quality of life in the communities in which they are located. …. The odor associated with CAFOs has had a detrimental effect on the quality of life of rural residents, and there may also be associated adverse health effects. Physicians in rural areas may be asked to assess patients with concerns related to neighboring CAFOs and may be drawn into a political battle regarding the authorization of the development of additional CAFOs."*

A range of studies have investigated the effect of odour on the neighboring communities. Some of the first reports of problems for residents in neighboring communities arose in USA in NC and Iowa (Thu et al., 1997; Schiffman 1998; Wing and Wolf 2000; Wing et al., 2008).

The range of complaints from urban dwellers in three communities from the study in NC by Wing and Wolf (2000) can be seen in table 5.1. It is relatively easy to see the severity of complaints related to odour stemming from hog operations. The study was based on two earlier studies from NC and Iowa by Schiffman et al. (1998) and Thu et al. (1997), respectively. These studies also investigated mental wellbeing, and Shiffman et al. (1997) found more depression and anger in the NC population whereas the Iowa study did not.

Table 5.1. Wing and Wolf (2000); Problems that affect respondents' own life or health according to the livestock in the community. Fishers exact test p< 0.05: * group vs None; ** Group vs Cattle.

Type of livestock Problem affecting respondent	None N = 50 n(%)	Cattle N = 50 n (%)	Hog N = 55 n (%)
Livestock odour	0	8 (16)*	25(45)*, **
Livestock odour (limits adult recreation)	0	0	14(25)*, **
Livestock odour (respiratory symptoms)	0	0	6(11)*, **
Livestock odour (can't open windows)	0	0	4(7)
Livestock effluent (contaminated well)	0	0	4(7)
Livestock odour (try not to breathe)	0	0	3(5)
Livestock odour (nausea)	0	0	3(5)
Livestock operation (flies and insects)	0	0	3(5)
Crop sprayers (dust or noise)	1(2)	0	2(4)

These studies were all performed in response to public complaints, and the two first were direct studies initiated with groups of concerned citizens. Even if the studies by Wing colleagues deliberately made random samples of different neighborhoods the studies were performed in a situation of concern and given that the exposure was obvious to the people interviewed, they were prone to be biased. The qualitative information from the studies, however, are a clear indicator of the complaints reported from residents living in livestock dense areas.

A range of reviews have summarized the situation in the literature, and they are mostly finding indications of health effects, but no clear cut causal relation between the exposure and effect due to the cross sectional design, the lack of objective measurements of environmental exposure and / or health outcomes. This leaves room for bias in reporting from the communities, and the practitioners working in these areas (Hoopmann et al., 2006; Heederik et al., 2007; Casey et al., 2015; Nachman et al., 2017; Douglas et al., 2018; O'Connor et al., 2017b, 2017a).

5.1.2 Comparison of the animal density in Denmark and The Netherlands

From Eurostat it is seen that the total animal units in NL is almost doubled compared to Denmark.

There is a greater number on km² arable land used to distribute the animals in DK. However, at the same time NL is exporting liquid manure to Belgium, France and Germany, which might decrease the exposure to farm emissions towards the Danish level in terms of manure deposited per area, see table 5.2.

Looking at the population density in the two countries there is a clear difference with app 3 times more persons per km² in NL. This means more people are exposed to the farming emissions in NL compared to DK.

This does not preclude local differences with a particular large CAFO in the two countries. The mean farm size in Denmark is higher than in The Netherlands meaning that the probability of such a problem is higher in Denmark.

Table 5.2. Comparison of the animal density in Denmark and The Netherlands using data from EUROSTAT.
•: 1 Hectare is equal to 0.01 square kilometer

For the year 2016	DK	NL
The number of animal Units per ha arable land	1.6	3.8
The number of animal Units per Km^2 arable land	160	380
The proportion of land used for farming	Ca 65% (excl forests)	57%
The country size Eurostat	44,493 km^2	41,198 km^2
The size of arable land	28,920	23,483
Total animal units over the arable land*	4.627.200	8.923.487
Population density per Km^2	134	411

6 Literature search

Extensive literature searches were performed including the last 30 years of published research, with a primary focus on studies among residents living in areas with intensive livestock farming concentrating on cows, pigs, sheep, goats and poultry farming, see figure 6.1.

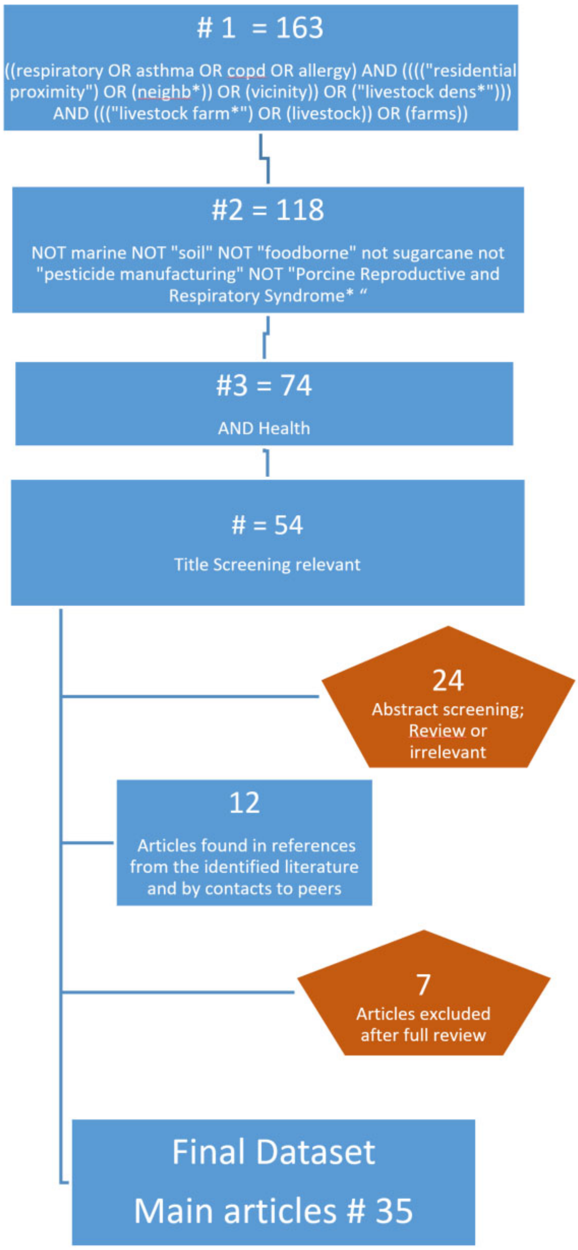

Figure 6.1 Search flow.

A literature search was performed in PubMed using the search terms;

Step 1 (result 163)

((respiratory OR asthma OR copd OR allergy) AND (((("residential proximity") OR (neighb*)) OR (vicinity)) OR ("livestock dens*"))) AND ((("livestock farm*") OR (livestock)) OR (farms))

Step 2 (result = 118)

Step 1 PLUS
NOT marine NOT "soil" NOT "foodborne" not sugarcane not "pesticide manufacturing" NOT "Porcine Reproductive and Respiratory Syndrome* "

Step 3 (result =74)

Step 2 AND Health

Step 4 (result = 54) Titles screened for relevance

Step 5 (result = 30)

Abstracts were screened and 24 were either reviews or irrelevant

Step 6 (result = 42)
Twelve articles suggested by peers or still not identified from the "Greenpeace list" were included

Step 7 (result = 35)
Finally 7 articles were excluded after full review.

The 35 articles included as primary literature are shown in Appendix 1 table 1. Table 2 is showing articles included as background information and table 3 is listing reviews.

7 Particles, aerosols and gasses emitted from CAFOs

A range of different components that give rise to exposures are emitted from farm operations and they consist of particulates and gasses. The particulates are a special mix consisting of fodder, fecal particulates, hair, skin particulates, micro-organisms and viruses, allergens etc. Due to these different components, the environmental particulate pollutants from AFOs (animal feeding operations) are quite different from those e.g. traffic emissions for gasses like ammonia (NH_3), hydrogen sulfide (H_2S), and carbon dioxide (CO_2). On top of these gasses and particles, a range of odorants being semi- and low-volatile components are emitted from the degrading biomass in the farms and manure from the animals. Emissions of components that give rise to exposure from farm operations is also seen during the application of manure from the manure storage on to the fields in order to be used as fertilizers, particularly in late winter and early spring. For ammonia, a special problem is chemical reactions of ammonia with acid gases and particles in the atmospheric environment producing secondary inorganic particles that are a part of the $PM_{2.5}$ particulates in ambient air. Thus farming contributes to the burden of disease by contributing to the general $PM_{2.5}$ exposure, which is often ignored or forgotten.

Depending on the meteorological conditions, emitted particles and gasses will be distributed following the wind direction in different heights and lengths away from the farm and create different exposures to the CAFO neighboring residents. Most of these exposures are not visible or obvious to the people who are exposed. However, the semi-volatile and low-volatile compounds that are emitted from the farm operations are easily detectable by people living in the surroundings of CAFOs and therefore being noticed by the residents in the areas around the farm operations.

The concentrations of the particles, toxins and gasses in the environment around the CAFOs are much lower than what is encountered inside the CAFOs by the farmers working with the farm animals. It is therefore still not fully elucidated if these concentrations are sufficient to induce health effects in neighboring residents either generally or in susceptible parts of the population.

7.1 Exposure assessment

In order to determine the exposure to the population a range of methods are used spanning from measurements in the environment at the home or in the neighborhood to models of exposure like Land-Use Regression (LUR), advanced physical-chemical models and dispersion modelling. These models are quite advanced as they often take into account the chemical processing in the atmosphere. Also very simple methods are used in many studies. These include the number and the distance to farm operations or the number of farms within a buffer zone, around the home.

The underlying assumption for this kind of exposure estimation is that the concentrations measured or estimated at the doorstep are representative for personal exposure.

7.1.1 Area level of exposure and exposure characteristics

A range of studies have measured farm exposures in the vicinity of farms. In the US, Thorne, Ansley, Perry et al. (2009) found mean endotoxin levels between 26 and 29 EU / m^3 160 m downward to pig farms, less than 1% of the mean concentrations within the stables, but with single measurements as high as 140 EU / m^3. In a German study, individuals living in a rural area with intensive animal production had increased endotoxin levels in their backyards, around 2 EU / m^3 (Schulze et al., 2006). In a study from Texas, US, Gibbs et al. (2004) concluded that bacteria and fungi were recovered inside and downwind of swine facilities, and for bacteria in levels that could cause potential human health hazard.This finding was supported by Green et al. (2006) in another study US, who found a marked increase in bacterial CFUs / m^3 inside the facility (18,132 CFU / m^3 average) compared to upwind (63 CFU / m^3 average), with a steady decline out to approximately 150 m downwind, where the total concentration of bacteria was 10% of the concentration just outside the CAFO, and only marginally higher than the upwind concentration. Guidry et al. (2017) measured hydrogen sulfide at three schools near industrial livestock facilities, and concluded that the hydrogen sulfide concentration increased with decreasing distance to livestock farms. All together existing studies support exposure levels close to livestock farms to be substantially lower than inside, but still far from negligible. Quite a few studies rely on the aggregated level of farm related characteristics e.g. farm density. This type of associations is considered low level of evidence. An example of this is the study of mortality in North Carolina in areas with different CAFO-density, acknowledged by the authors (Kravchenko et al., 2018). The advantage is that it is easy to perform. The disadvantage is that the exposure assessment is imprecise and prone to errors in the risk assessment caused by underlying parameters not accounted for at the individual level (so called ecological errors or ecological fallacy). These studies are indicative of a potential association at best but need to be followed by higher quality studies with exposure information and information on potentially confounding variables at the individual level.

7.1.2 Address based

The exposure assessment can be based on distance to the nearest animal farm as well as distance-weighted PM_{10} emissions from animal farms within 500 m distance to the nearest animal farm. This can also stratified for animal species and distance to the nearest stable with a specific animal type e.g. goats or swine.

Both individual exposure proxies (based on the above) and relative exposure proxies are considered by comparing two different areas, one with high density of animal farms and one with low.

In some studies, no parameters related to dispersion, deposition or transformation of airborne components are included, e.g. (van Dijk et al., 2017). Emissions are in this case addressed exclusively by linear dilution based on the inverse distance between home address and the point source.

The advantage of such an approach is the inclusion of data for animal types at the exact location. The disadvantages are related to the fact that physical and chemical processes that are important for the emission, transport, transformation, dispersion and deposition of components from animal farms are not taken into account, just as the actual composition of components is not addressed.

7.1.3 Land Use Regression (LUR)

Another way is to perform calculation of exposures by application of Land Use Regression (LUR) models. LUR is based on a combination of measurements and a number of local parameters and estimation of emissions of PM and other compounds, e.g. ammonium or endotoxins based on the production, number and type of animals (de Rooij et al., 2017). The exposure is based on a range of local parameters like: i) number of animals within buffer zones of e.g. 500 and 100 m around the address, ii) distance (and inverse distance and distance-weighted number of animals on the nearest farm) to the nearest animal farm and type of animal, iii) weekly mean values of temperature, pressure, radiation, wind speed, relative humidity, duration and amount of precipitation as well as hours of sunshine and wind direction can be applied. Measuring stations within close range of the nearest animal farm and "background" stations can be included as well. For de Rooij et al. (2017) this was not more than 500 m from the nearest animal farm.

The advantages of the LUR approach is that it is possible to utilise good data for different animal types and where they are located. Furthermore meteorological variations are taken into account to a limited extent using this approach.

A disadvantage of the approach is that LUR is not causal modeling, but based on pattern recognition. It can be quite accurate in reproducing patterns of high and low concentrations, but provides no opportunities to understand *why* they are high and low. Measurement averaging period is important in relation to characterizing the variations in e.g. PM_{10}, and if the averaging period is too long, it will make it difficult to separate the background level from the local signal. Furthermore the background station needs to be upstream and more than 500 m away from the area of interest. In the study by de Rooij et al. (2017), the averaging period is quite long (one week), and the location used for background measurements is probably located too close to the other animal farms to provide the needed information of background levels.

7.1.4 Deterministic modelling

Exposure assessment can be calculated using causal, deterministic transport and transformation models, typically of Gaussian plume design. Such models are driven by detailed meteorological data sets and incorporates data on emissions from point sources (e.g. stacks, manure storage etc.) and area sources (e.g. crops on fields, manure/slurry application etc.). These models base the airborne dispersion on the description of physical processes, such as transport, dispersion and deposition, and relevant theory (e.g. boundary layer height and mixing), and takes other relevant parameters into account (e.g. land use data).

In a study by Boers et al. (2016) the exposure assessment to odour is determined on the basis of calculations with the local Dutch dispersion model STACKS. The results are given for the 98th percentile of hourly values for odour concentration, corresponding to the method applied by the Dutch authorities in relation to odour.

Another study by Blanes-Vidal et al. (2014) calculated overall exposure to concentrations of NH_3 from the main significant sources within a designated study area on the individual household level using a combination of a long-range transport model to account for the background concentration level, and the Danish local-scale transport and deposition model OML-DEP, which also accounts for the chemical transformation of NH_3 to NH_4^+. The Blanes-Vidal et al. (2014) study hypothesized that NH_3 concentrations can be applied as a proxy for airborne exposure to odours and used inverse distance weighting multivariate interpolation to estimate household concentrations from the model results, which were calculated on a 400 m x 400 m grid.

The advantages of deterministic modelling is that it provides a deeper understanding of causality and processes governing the pathway from emission to exposure.

Disadvantages of this method can be that it is sometimes difficult to obtain all relevant input data for the model. It can e.g. be difficult to obtain data for area source emissions, (which is the case in the Boers et al. (2016) study), and in this way some of the exposure will be missing, as area source emissions can make a significant (short-term) contribution when applying manure / slurry to fields.

8 Health effects

8.1 Odour

The first study to report problems with odour from CAFOs was Wing and Wolf (2000) studying the complaints in three poor communities in North Carolina. The hog and cattle study areas were defined by a < 2-mile radius around the operations and each study area was contained within a single census block group. The hog operation was a feeder-to-finish facility with a head capacity of approximately 6,000, a steady-state live weight of approximately 800,000 pounds, and one liquid manure lagoon. The cattle community contained two neighboring dairy operations with a combined head capacity of approximately 300, live weight of approximately 200,000 pounds, and two lagoons. The area without intensive livestock operations extended across two block groups. Parts of two block groups were included to ensure that eligible households were at least 2 miles away from any livestock operation using a liquid waste management system.

In the hog exposed area the following complaints were found in excess (See table 5.1): odour limits outdoor recreation, odour induces respiratory symptoms. Also the group with the hog operation in the area reported: "*can't open windows due to odor, try not to breathe due to odor and nausea due to odor*" to some extent, however these were not significantly increased. As this was a study created after a public complaint about the odour in the community it is prone to a bias towards over reporting. However, as a qualitative study on the complaint profile it shows interesting trends and also it shows that hog operations seem to be more "annoying " compared to cattle operations.

In the NiLS study in Lower Saxony (D) Radon and colleagues investigated the 4,537 inhabitants, age 18–44 years, living in a rural town. They received a mail-in questionnaire and of these 69% (3112) with a mean age of 33 returned a filled-in form (Radon et al., 2004). Physical Short Form (SF)- and emotional SF-scores decreased significantly in an exposure related way. SF12 physical wellbeing vs odour was studied in multiple linear regression analyses: a little RR (Risk Ratio) (95%c.i.)-0.66 (-1.16 to -0.16), very much -1.35 (-2.16 to -1.35) and extremely bothered -3.47 (-4.66 to -2.28) for SF12 Emotional wellbeing vs odour a little RR (95%c.i.) -1.12 (-1.83 to -0.40), very much -2.27 (-3.43 to -1.11) and extremely bothered -2.56 (-4.25 to -0.87). The estimates were corrected for age, gender, smoking habits, level of education, current living on a farm, nasal allergies, and time spent per week in the home environment.

Two studies from Denmark investigated 454 persons from 1120 households (participation rate 45%) from six 12 km × 12 km non-urban Danish areas. Ammonia concentrations at each household were estimated by inverse distance weighting (IDW) multivariate interpolation, from UTM coordinates and OML-DEP modeling results. Ammonia, NH_3 was calculated by the Danish Eulerian long-range transport model DEHM and the local-scale transport deposition model OML-DEP. In the first study (Blanes-Vidal, Baelum, Nadimi, et al., 2014) showed how the probability of annoyance rose with increasing NH_3 exposure, and that the increase happened between 0.1 – 10 $\mu g/m^3$, fig 8.1 Multinomial models controlled for person-related variables showed that the odds for a citizen of being "slightly annoyed" by environmental odors (compared to not being annoyed) significantly increased with

NH_3 concentration at the residence (ORadj = 2.86; 95% CI = 1.84–4.44), for each unit increase in $\log_e$ (NH_3 exposure). Higher NH_3 exposure also increased the odds of being "moderately annoyed" (ORadj 8.77, CI (3.53–21.8) and "very or extremely annoyed" 13.4 (4.34–41.2) age, gender, smoking habit, job (occupation), time spent at home per week, existence of household residents below 18 years old, and years living in the area.

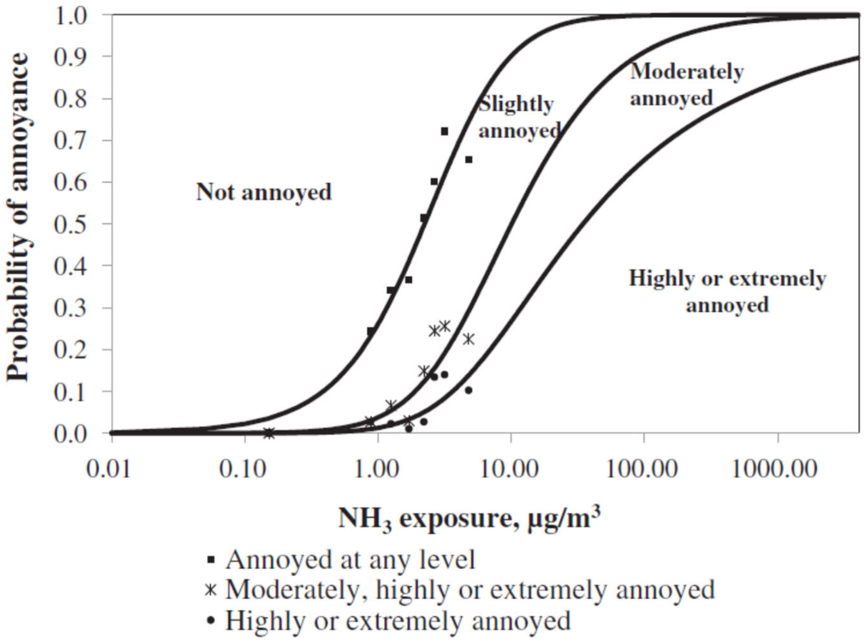

Figure 8.1. The association between NH# exposure and annoyance in Danish citizens living in rural areas, (Blanes-Vidal et al., 2014).

In a mediation analysis the authors studied the mediation effect of the three domains annoyance, health risk perception, and behavioral interference. They found the effect of exposure on behavioral interference to be almost completely (81%) mediated by annoyance with an indirect effect on behavioral interference (38%) and the exposure-health risk was only mediated by annoyance (44%).

In the Second analysis (Blanes-Vidal, Baelum, Schwartz et al., 2014) the authors investigated the association between respiratory symptoms and $\log_e$ (NH_3 exposure) and found OR (Odds Ratio) (95 % c.i.) for ''itching, dryness or irritation of eyes'' of 1.69 (1.1–2.6), ''itching, dryness or irritation of the nose'' of 1.35 (0.87–2.11),''runny nose'' of 1.25 (0.9–1.8), ''cough'' 1.75 (1.1–2.7), ''chest wheezing or whistling'' 1.7 (0.9–3.4) and ''difficulty breathing''1.34 (0.6–2.9). All of the symptoms were associated to odour annoyance. In the next step the authors performed a formal mediation analysis to test whether a mediation structure in the data was possible. The results were compatible with the hypothesis that odour annoyance acts as mediator of the effect of exposure on symptoms, either fully or partially. Only indirect effects (full mediation) were found for nasal symptoms, whereas eye symptoms and cough were directly as well as indirectly associated (partial mediation).

Hooiveld et al. (2015) studied 753 participants (42-44% of invited) living in an area with high density of animal feeding operations (AFOs) mostly with cattle, pigs and poultry (Hooiveld et al., 2015). Participants' residential addresses were geocoded, and distances between the home address and all AFOs within a 500 m radius were calculated by ArcGIS. Odour annoyance in the neighborhood was negatively associated with general health (OR: 95%CI) 0.73 (0.53-

0.99) and a higher number of reported respiratory 1.22 (1.07–1.38), gastrointestinal 1.40 (1.21–1.62) symptoms.

A study of 582 residents neighboring livestock farms in the southern part of the Netherlands used the STARKS dispersion model and expressed odor at the 98th percentile of hourly odour concentrations, pairing the private residence with the nearest farm (Boers et al., 2016). Odor annoyance was determined by two questions in the questionnaire using closed VAS-scales. Association between "livestock stable" odor exposure and reporting of: i) odor annoyance from livestock housings OR (95 % c.i.) 2.19 (1.49–3.23) ii) odor annoyance from spreading slurry and manure 1.60 (1.27–2.01) iii) livestock farming in general 1.92 (1.53–2.41). Other explanatory factors e.g. age, education and occurrence of air pollution in the environment were independently associated with odour annoyance, but no evidence of confounding or effect modification by these factors were found.

8.1.1 Summary of findings

The different studies of odour have all been showing more symptoms, with increasing odour perception, in the population. From the first studies, it seems plausible to deduct that the odour annoyance is higher in hog operations compared to cattle and other animal operations. The NiLS study employed SF12 questionnaires for physical as well as for emotional wellbeing and found negative influences of odour on both variables in an exposure risk response fashion. The same was seen in the Dutch study in a high density live-stock area. In this study, the exposure to odour was corrected for confounders and the full model showed, that the odour annoyance was negatively associated with general health-, respiratory- and gastrointestinal symptoms. Finally, the study of Boers et al. (2016) showed that the odour annoyance was related to self-reporting of odour from livestock housing and odour annoyance from the spreading of manure as well as from livestock farming in general. For all these studies, it is characteristic that their design is cross sectional and therefore prone to bias. Further, it is really difficult to study the effect of an exposure that is so easily detected by the exposed people and actually offensive to the people's olfactory system. Hence from these studies it can be deduced that odour is an annoying entity in the environment. However, it is difficult to interpret the association between the odour strength and health complaints. The mediation analyses in the studies by Blanes-Vidal et al. (2014) is pointing towards possible direct effects of the NH_3 on respiratory effects. The authors state that these effects could be explained by either NH_3 being a marker of a general exposure to organic pollutants from farming e.g. endotoxin or an effect of reverse causation i.e. exposure → symptoms → annoyance.

8.2 Respiratory disease, symptoms and biomarkers

In one of the first studies of the health effects on neighbors of CAFOs from Niedersachsen, the NiLS study included 3867 (5965) children aged 5-8 years from a regional survey were selected to represent the population living in rural areas with high intensity farming. Using modeled endotoxin in the outdoor air it was shown that for children with atopic parents the modeled log endotoxin load of non-atopic asthma was increased in the group of children with atopic parents OR 1.64 p =0.02. Atopic asthma was non-significantly negatively associated to log endotoxin load with ORs from 0.74 – 0.73 P> 0.09 (Hoopmann et al., 2006).

Mirabelli et al. (2006) studied 225 of 449 rural schools in a nation-wide study of middle schools in NC. In total 58,169 of (73,305) = 79% of the children at the schools responded to a questionnaire about respiratory symptoms. Exposure was estimated as (1) distance to nearest CAFO from the school address, (2) Steady state live weight (SSLW) within 3 miles and (3) a weighted SSLW based on distance and size of nearby swine CAFOs. The prevalence ratio for respiratory symptoms among children from schools with a CAFO < 3 miles away compared to children from schools with the nearest CAFO 3 miles or more away. The study found increased prevalences for several complaints among allergic children from the schools with a CAFO < 3 miles away: PR (95% c.i.) for "Current wheeze" 1.05(1.0–1.1), for "General practitioner (GP) visits for asthma" 1.06 1.0–1.1), for "Asthma medication" 1.09(1.0–1.2) and for "Activity limit" 1.09 (1.0-1.2). Confounders included in the analysis were: age, race, socioeconomic status, smoking, school exposures, and household exposures.

As part of the NiLS study (Radon et al., 2007) one town in the study area was chosen for a thorough examination of health and ammonia exposure (Schulze et al., 2011). In the town chosen for the ammonia measurements, 457 nonfarm subjects filled out the questionnaire. Of these, 218 subjects were invited to participate and 149 subjects aged 18-44 years took part in the clinical examination. Analyses were adjusted for age, sex, smoking habits, environmental tobacco smoke, level of education, number of siblings, and parental atopy. ORs according to ammonia exposure using the first quartile >19.71 $\mu g/m^3$ as cut of. No effect of residential NH_3 was found for neither "Wheezing without a cold" OR (95% c.i.) 1.36 (0.66-2.82) nor "Allergic rhinitis" 1.15 (0.57-2.35).

Schinasi et al. (2011) studied the health effects related to air pollution and self-reported odor in 101persons living within 1.5 miles of pig operations in 16 counties of North Carolina USA. The recruitment for the study was done via community organisations (Concerned Citizens). The participants were instructed to register odour and symptoms every 12 hour during two week periods. A range of symptoms are found in relation to odour and H_2S concentrations however statistical power is low, and no unequivocal associations are found. There is no information on the selection occuring other important predictors of susceptibility. However, the authors report, that contrary to what is found in most studies there was a higher proportion of participants who grew up on a farm reporting hay fever (42%) compared to other participants (19%), which indicate a possible selection of more susceptible persons into the group recruited.

Wing et al. (2014) studied symptoms among persons in three areas with two different swine CAFO treated sewage sludge (TSS) areas i) liquid and ii) cake systems and one control area without TSS. In all 341 participants were recruited 157 (of 212) from the liquid TSS area, 85(of 101) from the cake TSS area and 188 (of 286) from the comparison area were included. Gastrointestinal and dermatologic symptoms were more frequently reported in areas with odours from liquid TSS and cake TSS compared to comparison areas. Lower respiratory symptoms were also more frequent in areas with odour from TSS than comparison areas. None of the associations reached statistical significance. Lower respiratory symptoms were found significantly more frequent (Wing et al., 2014) among residents who reported livestock odor compared to participants who reported no or faint livestock odor. Difficulty breathing PR (95% c.i.) 1.52 (1.02, 2.27) and cough 1.31 (1.01, 1.71).

Hooiveld et al. (2015) studied 753 participants (42-44% of invited) living in an area with high density of animal feeding operations (AFOs) mostly with cattle, pigs and poultry. Participants' residential addresses were geocoded, and distances between the home address and all AFOs within a 500 m radius were calculated by ArcGIS. Odour annoyance in the neighborhood was negatively associated with general health (OR: 95%CI) 0.73 (0.53- 0.99) and a higher number of reported respiratory 1.22 (1.07–1.38), gastrointestinal 1.40 (1.21–1.62) symptoms.

A cross sectional study by Borlée et al. (2017, 2019) found an inverse association between different indicators of livestock farm exposure and self-reported current asthma and COPD (Chronic Obstructive Pulmonary Disease). This could indicate a protective effect of farming or a self-selection away from farming areas among patients. Among COPD patients wheezing during the last 12 months vs distance to the nearest farm (quartiles) was increased when living closer to farms, but not in a dose dependent manner OR (95% c.i.) 450–640 m 2.17 (1.32–3.57), 290–450 m 1.65 (1.05–2.59) and <290 m 1.45 (0.90–2.35). Living with >11 vs <4 farms within 1000 m 1.71 (1.01–2.89). Analyses were adjusted for age, sex and smoking habits (Borlée et al., 2017). A later analysis on the same data showed the associations found in the study were not influenced by the attitude towards live-stock farming (Borlée et al., 2019).

Schultz and colleagues (2019) selected 1547 rural non-farmers from a general health survey (Survey of the Health of Wisconsin, SHOW) conducted in the period 2008-16. The general screening allowed for confounder control for gender, age, BMI, smoking status, education, income and pet ownership. Current allergies of any type and nasal allergies were 2.5 times higher at 1 mile from a CAFO, and decreased to 1.3 times higher at 3 miles from a CAFO when compared to 5 miles from a CAFO. Lung allergies remained 2.2–2.6 times higher at distances 1–3 miles from a CAFO when compared to 5 miles. Asthma and asthma control measures, including one or more asthma attacks in the last 12 months or taking asthma medication. Reporting current asthma was consistently about 1.8–1.9 times greater among those living 1–3 miles versus 5 miles from a CAFO (Figure 3). The odds of ever being diagnosed with asthma was 3.11 (95% CI: 1.49, 4.36) and 2.67 (95% CI: 1.33, 3.08) when comparing 1 and 1.5 miles from a CAFO to 5 miles from a CAFO. Similar to the associations seen with current and nasal-specific allergies, the odds of doctor diagnosed asthma and asthma medication use decreased as distance from a CAFO increased. Those living 1, 1.5, 2, 2.5 miles from a CAFO, asthma medication was 4, 3, 2.5, and 2 times greater, respectively, when compared to those living 5 miles from a CAFO; all associations statistically significant. Odds of an asthma attack were consistently 2-fold higher at 1–3 miles versus 5 miles from a CAFO, with the odds being 2.34 (95% CI: 1.11, 4.92) times higher at 1.5 miles versus 5 miles from a CAFO.

The VGO study (de Rooij et al., 2019) studied 2494 persons (35%) aged 18-72 years adjusted for age, sex and smoking habits. Wheeze + SOB (shortness of breath) and daily cough were significantly associated to increasing levels of endotoxin modeled with the LUR or the dispersion model and wheeze + SOB was related to the number of farms in a 100m zone around the residence. Current asthma was significantly associated to increasing levels of endotoxin modeled with the LUR or the dispersion model and with the PM_{10} level. However, asthma decreased with decreasing distance to the nearest farm. COPD was negatively associated with the proximity to the nearest farm. The dispersion modelling results were in agreement with measurements at 61 locations as part of a validation exercise.

General morbidity and mortality

A register based study using morbidity information from GP registries investigated a range of health effects related to farm exposures (van Dijk, Smit, et al., 2016). The study included 54.777 persons / 144,984 person years (16 general practices) in an area with high density of livestock farming. Participants were followed for 7 consecutive years for 26 different self-reported symptoms including four respiratory (cold / flu, cough, shortness of breath / difficulty breathing and sore throat) in the last month. Diagnoses of health conditions associated with livestock exposure in earlier studies were included (ICD code): lower respiratory tract infections (R81-R83), pneumonia (R81), upper respiratory tract infections (R74-R78), respiratory symptoms (R02, R03 & R05), asthma (R96), chronic bronchitis / bronchiectasis (R91 40 years and older), emphysema / COPD (R95 e 40 years and older)), allergic rhinitis (R97), depression (P03 & P76), constitutional eczema (S87), vertiginous syndrome (H82), vertigo / dizziness (N17), gastro-intestinal infections (D73), chronic enteritis / ulcerative colitis (D94). All analyses were adjusted for age and gender. Individual parameters like smoking habits, socioeconomic status and occupational exposure were not available from the registries. Generally, there were lower risks of medical conditions associated with estimates of farming exposure.

From the VGO study 1828 COPD patients were followed in for comorbidities via electronic patient records for the year 2012. The exposure was based on residential address, and the distance to as well of type of the nearest farm. The study found when comparing to people living >500m from the nearest farm the number of comorbidities below 250m: OR(95% c.i.) 0.8 (0.7–0.98), & 250-500m 0.9 (0.8–1.03). For respiratory symptoms: < 250 m 0.6 (0.4–0.98) & 250-500m 0.8 (0.5–1.1). In this study the only confounder control available was age and gender. Hence the authors conclude, that the study "showed no convincing evidence for an association between livestock exposure and the examined health outcomes" (Baliatsas et al., 2017).

A study of mortality, hospital admissions, and emergency department (ED) usage in two different areas in North Carolina (Kravchenko et al., 2018). The area was divided into case- and control areas: i) 2.3 mio in the case area Ca; with CAFOs ; ii) CaHigh; a subset of 0.4 mio living in an area with > 215 hogs / km^2, and iii) Control 7.3 mio living outside the CAFO area. The outcome studied were mortality, hospital admissions, and emergency department (ED) usage for health conditions potentially associated with hog CAFOs. In the case area anemia, kidney disease, infectious diseases, and low birth weight were higher compared to the control area. For the CaHigh area the OR for a range of conditions were significantly increased: anemia OR 1.5; kidney disease 1.3; septicemia 2.3 and for tuberculosis 2.2. The study was purely registry based, and thus not able to account for individual measurements on environmental contaminants, biomarkers of exposures and especially socioeconomic factors, and differences in residential and occupational locations. Hence, no inference on causality could be made.

8.2.2 Susceptible groups

Asthmatic patients

A clinical population from a rural area in Pennsylvania included 35,269 asthma patients of all ages (5-75+) who were followed for exacerbations from 2005-2012 (Rasmussen et al., 2017). Asthma excercebations were defined as hospitalizations, emergency encounters and new oral corticosteroid orders (from 2008-12 only). For each type of asthma exacerbation, asthma patients with at least one exacerbation was compared to subjects with no exacerbations. Proximity to CAFO 0-4.8km and > 4.8km (3 miles). Covariates in the adjusted model included those created using the electronic patient health record: age category, year, sex, ethnicity, season, smoking status, family history of asthma, overweight / obesity, socioeconomic status (SES), type 2 diabetes, distance to nearest major and minor road and community socioeconomic status. In adjusted models, proximity to CAFOs was associated to oral corticosteroid orders ORC 1.1 (1.04–1.2), to emergency encounters 1.1 (0.9–1.4) and hospitalizations 1.3 (1.2–1.5).

Three studies from an agricultural area in Washington State with intensive farming production were performed on asthmatic children. The area of approximately 300 square miles is characterized by a high density of large-scale animal feeding operations, (Loftus, Yost, Sampson, Torres et al., 2015; Loftus, Yost, Sampson, Arias et al., 2015; Loftus et al., 2020). Exposure estimation was based on the first study of 58 school aged children (avg 10 years) exploring the effects of $PM_{2.5}$ measured as regional 24-hour average $PM_{2.5}$ measured at a single air monitor located centrally in the study region. Odds of specific asthma symptoms associated with an IQR increase in weekly $PM_{2.5}$:

Symptom or medication use	OR (95%CI)
Limitation of activities	1.21 (1.00, 1.46)
Wheezing	1.31 (1.18, 1.45)
Nighttime waking	1.13 (1.01, 1.26)
Shortness of breath	1.10 (0.96, 1.26)
Symptoms worse in morning	1.00 (0.91, 1.11)
Use of “relief” medication	1.09 (0.99, 1.20)

Confounders included were age, BMI, inhaled corticosteroid use at baseline, and sex.

In the following analysis including 51 children the exposure was estimated as 24-hour ammonia concentrations. Using a spatially representative approach, a network of 14 devices were deployed outside subject residences (27%) in the 20 * 60 km study region to collect 24 hours samples every six days (Armstrong et al., 2013). The concentrations varied from 0.2 to 238 µg / m^3, and had a strong correlation with proximity to animal feeding operations.

No association was found for asthma symptoms or medication and the NH_3 concentration. Covariates included in models were temperature and relative humidity (averaged over the week prior), days elapsed in study and seasonality. Also included were subject-specific characteristics potentially associated with asthma: sex, age, atopy, use of inhaled corticosteroids at baseline, body mass index at baseline, and the presence of adult smokers in household.

In a later re-analysis studying 16 of the 51 children for changes in an inflammatory marker, leukotriene E4 (LTE4). The children delivered a “spot” urine sample every morning six days over 14 weeks. This was used to study the urine uLTE4. Exposure estimates accounted for exposures at both home and school by modeling exposure at both locations for each child and time-averaging based on school schedules. The daily exposure to ammonia was estimate with a plume model based on distance to CAFOs, farm size, and daily wind speed and direction. The model was validated against direct measurements of ammonia biweekly at 18 sites across the region for 14 months (Armstrong et al., 2013). The authors found a borderline increase in uLTE4 (ug / mg creatinine) of 0.17 (−0.01‑ 0.35) after days with elevated NH_3 concentrations.

COPD patients

From GPs located in rural areas electronic medical records during 2006–2012 were used to follow asthma (AST) and COPD patients aged 7–40. From the area with a high density of livestock farms 2546 AST / 899 COPD were included and from the area with lower density of livestock farms 2310 AST / 933 COPD were included(van Dijk, Garcia-Aymerich et al., 2016). Exacerbations were identified via prescriptions for medication relevant for AST and COPD respectively. Exacerbation rates of COPD were higher in areas with high density farming compared to lower density farming IRR (95% c.i.) 1.3 (1.1–1.6),for patients living within 500 m of poultry farms 1.4 (1.03–1.8). For asthma no difference was found between patients in the two areas.

A recent study from the Dutch VGO program investigated the daily morning and evening lung function in a selected group of non-smoking COPD patients. From the medical examination 213 COPD patients with a good spirometry performance according to ATS / ERS criteria were invited to participate in a 3 month long testing of lung function plus an online questionnaire morning and evening (van Kersen et al., 2020). Exposure was estimated from the average daily ambient levels of NH_3 and PM_{10} from two nearest measuring stations of the Dutch Air Quality Monitoring Network and ambient temperature and relative Humidity from the Dutch Meteorological Institute. Participants recorded daily livestock-related odour annoyance on a scale from 0-10. Only weak or missing effects were seen for symptoms and the association to odour.

Summary of finding

The results from the different studies are not coherent but the high quality studies actually seem to convey a protective effect of farming on the general population for asthma.

The VGO project showed in the study from (2017), after adjusting for age, sex and smoking habits an inverse association between indicators of livestock farms and self-reported current asthma as well as COPD indicating a protective effect of farming.

Another study from the Dutch group showed a negative association with a range of farm indicators, farm exposure indicators and of respiratory tract infections, respiratory symptoms, asthma, COPD, and allergic rhinitis in a population studied by the use of GPs contact profiles with no clear pattern of exposure response variation. The studies are all cross sectional and lack objective measures of the health outcomes, hence they are prone to biases due to both participants and GPs knowing that they live close to farms. It is therefore not clear from these studies how the respiratory symptoms or diseases are related to indirect farming exposure.

Three studies stand out, because they have been performed in populations without the involvement of persons in the discussion about farming areas. This is from Hooiveld in Netherlands, Rasmussen in Pennsylvania and Schulz in Wisconsin. The Dutch study shows protective effects of farming in comparison with the use of general practitioners for respiratory conditions, whereas the Pennsylvania study showed that among asthma patients there was an increased risk for hospitalization as well as medication use associated to CAFOs in the nearby environment (4.8km), and Wisconsin study showed that respiratory complaints were higher in the areas with CAFOs compared to areas without high intensity farming operations and in the latter study reporting that recurrent asthma was consistently increased from 1.8 to 1.9 times among those living 1-3 miles away from a CAFO compared to people living five miles or more from a CAFO. The same was the case for being diagnosed with asthma. Finally, the study from de Rooij et al., 2019 showed that when using an exposure model for endotoxin they could show a significant increase in current asthma significantly associated to higher levels of endotoxin and the PM_{10} level. However, asthma decreased with decreasing distance to nearest farm, and the same was seen for COPD. This is emphasizing the importance of better measurements of farm exposure rather than just being close to a farm.

Of the two studies on general morbidity and mortality one is finding increased morbidity and mortality in the North Carolina population exposed to hogs. Contrary to this, the Dutch study is showing lower morbidity for a range of health outcomes in the CAFO exposed areas compared to the non-farming area.

For the panel studies with susceptible populations no associations are seen between ammonia exposure and respiratory symptoms neither in the asthmatic children nor in the COPD patients. However, a clear effect of weekly $PM_{2.5}$ exposure is seen among the asthmatic children. This is making the inference difficult, since the suspected marker of local farm exposure, ammonia, is not associated. At the same time the fine particulates being a mix of locally produced and long transported PM, which is related to farming as well as traffic is showing a significant association to symptomatology in the asthmatic children. However, it is not possible from the measurements to distinguish between farm, and traffic associated PM.

8.2.3 Respiratory infections

Hooiveld et al. (2016) studied in a second study contact to general praxis (GP) for people living in an area with high intensity of livestock farming. All contacts to GPs during 2009 were included in the study for 110,036 persons and compared the contact pattern in this area with the pattern for 78,060 inhabitants of a similar area with low farming intensity. The differences in the disease prevalence were mainly seen for infectious diseases with OR (95% c.i.) for pneumonia 1.42 (1.12-1.82) and for other infectious disease 1.42 (1.12-1.82) and chronic enteritis a borderline increase of 1.33 (0.99-1.79). But also for atopic eczema an increased prevalence appeared of 1.75 (1.05-1.79). Asthma and COPD prevalences were not different between the areas except a non-significant increase in asthma among children aged 0-4 year 1.32 (0.89-1.95) in 2009 and 1.23 (0.83-1.83) if a three year prevalence was used 2007-09.

Using number of CAFOs in postal code areas and health problems within the high CAFO density region, for goats only other infectious disease were increased to 1.87 (1.11-3.13). For COPD the number of CAFOs in the postal code was associated with an increase from 1.07 (1.01-1.14) in the age group 45 years and older to 1.13 (1.02-1.24) in the 60+ year olds.

The analyses were adjusted for registry duration, age, gender and SES, and at the postal code area level, additional adjustments were made for the number of inhabitants and total surface area. From the registries, it was not possible to control for personal characteristics like smoking and atopy.

In a registry based follow up of 140 thousand GP patients Kalkovska et al. (2018) found a decreasing risk of pneumonia with proximity to Poultry <1 km 0.15 (0.03-0.16), Goats <2 km Risk 0.28 (0.12-0.52), and the group calculated the population attributable fraction to be around 7% for pneumonia. However, due to the type of study, it was not possible to control for important confounders as history of tobacco use and socioeconomic status.

In another study of patients with overlapping diagnoses of asthma and COPD 425 patients aged 40 or more and diagnosed with both diseases were studied for their diagnosed conditions during 2012 (Baliatsas et al., 2019). Patients possibly working or residing on a farm (defined as a distance of < 50 m between house address and the closest farm) were not included. An increased risk for pneumonia of OR (95% C.I.) 2.5 (1.5-5.8) was found for patients living closer than 500 m to the nearest cattle farm. On the other side a decreased risk of any comorbidity of 0.4 (0.2–0.8) was found for patients living near (< 500 m), from a pig stable

In the study by van Dijk (2016) 16 general practices in an area with high density of livestock farming were delivering a complete list of their patient contacts. Infections were registered, of the total of 54,777 persons (144,984 person years). The highest category of poultry exposure within 500 m was related to acute respiratory infections RR (95 %CI) 1.17(1.06–1.29).

In a later follow up study of the same population as in (van Dijk et al., 2017; Borlée et al., 2015) Baliatsa et al. (2020) 117 thousand residents in “livestock dense area” and 86 thousand in a control area. Generally, there was no difference in chronic conditions. However, acute respiratory infections and respiratory symptoms as well as prescription roles for broad-spectrum antibiotics were more common in the livestock dense area. For pneumonia the OR (95% C.I.) were 1.45 (1.00–2.10) 1.58 (1.09–2.30) 1.60 (1.13–2.28) in 2014, 15 & 16, respectively. For Lower respiratory tract infections the values for the corresponding years were 1.31 (0.94–1.83); 1.44 (1.01–2.05) and 1.46 (1.03–2.05). For Cough, shortness of breath / dyspnea, wheezing the ORs were 1.14 (0.90–1.45); 1.27 (1.03–1.57) and 1.27 (0.98–1.66) during the three years. For COPD patients the same increase was seen. However, the ORs were for the three conditions were approximately 1.7; 1.6 & 1.4 respectively. Bronchopneumonia was generally more common among children in the livestock dense and significantly so in 2016 after adjusting for SES OR (95% C.I.) 2.2 (1.2–3.9).

In a study of patients hospitalized with pneumonia Smit et al. (2017) used kernel analysis and residential distance to poultry farm to investigate risk of pneumonia. The study found that living near poultry (< 1.15 km) farms was associated with an increased risk of pneumonia. The oropharyngeal microbiota composition among these cases differed from other pneumonia patients living >1.15 km from poultry farms with abundance of *Str. pneumoniae*. This is of interest because the outcomes suggest that high dust exposure of individuals living near poultry farms are more susceptible to develop pneumonia from human (non-zoonotic) commensal pathogens.

To follow up earlier reports of Q-fever and pneumonia related to goat farming the VGO group made a study of pneumonia in 2494 persons (35%) aged 18-72 years. They adjusted for age, sex and smoking habits and comorbidities (Freidl et al., 2017). Residents living close to (<2,000 m) a farm with 50+ goats had an increased risk of pneumonia of 1.9 (1.4-2.6) increasing to 4.4(2.0-9.8) (<500 m).

8.2.4 Summary of findings

An interesting observation from the study of Hooiveld et al. is the increase in COPD with a number of CAFOs in a postal code. It is highly interesting that the odds ratio goes up with increasing age with a 7% to 13% increase among 45+ year old and 60+ year olds, respectively. This could be an indicator of an effect of the farming intensity on chronic respiratory diseases. Another important observation is the study by van Dijk showing that the highest category of poultry exposure was related to respiratory infections with an odds ratio of 1.17. Following up on this study, Smit et al. used the current analysis with residential distance to poultry farm to investigate pneumonia in people hospitalized for this, and they found that living less than 1.15 kilometers from the nearest poultry farm increased the risk of pneumonia. Further they found that this pneumonia was increasingly caused by *Streptococcus pneumonia*. When following up the reports on Q-fever and pneumonia in the community, the Dutch study found that people living closer to big goat farms have an increased risk of pneumonia of almost twofold compared to people living further away and being doubled when the limit was set to 500 meters indicating a dose response association. Although all studies are cross sectional, there is a clear picture showing associations between farming operations in the vicinity, and pneumonia in the exposed population. This is confirmed for goat farms in a meta-analysis of all available studies (Post et al., 2019). However, the observed risk earlier associated to poultry farms was not confirmed.

8.3 Allergy

The NiLS Study in Lower Saxony, D, Radon and colleagues investigated the health among 1076 non farmers living in pig producing rural communities (Radon et al., 2007). The allergy testing comprised specific IgE for a panel of common allergens: grass, mugwort, birch, house dust mite (Der p), cat, dog, Cladosporium herbarum and Aspergillus fumigatus and farming allergens: rye, chicken, pig, turkey. Sensitization to common allergens did not change with the number of farms in the 500 m zone from the residence, when adjusting for age, sex, active and passive smoke exposure, level of education, number of siblings, and parental allergies. A study from the Alpine region investigated exposure to endotoxin between rural inhabitants (von Mutius et al., 2000). The study found higher endotoxin concentrations in mattress dust from farm children and from other rural children with regular farm contact, compared to children from the same villages without regular farm contact. Hence showing other routes of exposure than airborne spread of dust.

The study from Wisconsin by Schultz et al. (2019) including 1547 rural non-farmers from the general health survey on allergy conducted in the period

2008-16 found self-reported allergies to be more prevalent in the farming area. Current allergies of any type and nasal allergies were 2.5 times higher at 1 mile from a CAFO, and decreased to 1.3 times higher at 3 miles from a CAFO when compared to 5 miles from a CAFO.

The VGO project situated in a high intensity farming area with a mix of different operations (de Rooij et al., 2019) studied atopic sensitization using a combination of specific IgE > 0.35 U / ml to 6 common allergens: cat, dog, grass and house dust mite. Atopy was defined as a reaction to any common allergens and / or a total IgE higher than 100 IU / ml. Controlling for sex, age, smoking habits, education (high versus middle / low education), born in study area, and history of living on a farm during childhood the study demonstrated a negative association between atopy and dispersion modelled endotoxin (EU / m^3). The analyses also found a significant decline in atopy with shorter distance to the nearest farm.

8.3.1 Summary of findings

Of the three studies only the VGO study identifies factors associated to lower rates of atopy. As the study designs are rather similar, the explanation must rely on different assessment methods for allergy, a better exposure assessment, or a different environment – the VGO study is a high intensity farming area with a mix of different operations, whereas the NiLS study is from Lower Saxony, an area dominated by pig farm and Wisconsin is dominated by dairy farms. Another significant difference might be the confounders included. Rooij et al. control for a farming childhood, which has been shown to affect the sensitization rate well into adult age (Elholm et al., 2018). Further, it corroborates with the finding, that farmers and rural persons have lower sensitization rates for common allergens (Sigsgaard et al., 2020; Basinas et al., 2012; Elholm et al., 2016).

8.4 Lung function

Several studies investigated the effect of exposure to CAFOs on lung function.

In the NiLS Study in Lower Saxony, D, Radon and colleagues investigated the health among 1076 non farmers living in pig producing rural communities with spirometry and nonspecific bronchial hyper-responsiveness testing (NSBH testing). Among persons living with 12+ farms in a 500 m radius (Radon et al., 2005) from the home, FEV_1 was significantly lower than predicted -7.4% (-14.4 to -0.4). FVC, FEV_1 / FVC ratio and NSBH was not different from predicted (Radon et al., 2007). A few (32) measurements of endotoxin were sampled, these results correlated well with the number of farms in the vicinity of one town. However, the number of samples did not allow a formal testing of a possible health effect mediated by endotoxin in the air.

The same group performed a later study combined with measurements of ammonia over a year, and here they studied persons exposed to high versus low ammonia exposure. High; As being exposed to a mean yearly "interpolated ammonia exposure" of ≥19.71 µg / m^3 at their address. The study showed a decrease in FEV1 (% predicted) -8.19 (-13.71.-2.67) but no effect on FEV1 / FVC (Schulze et al., 2011).

A short 2 week panel study in non-smoking volunteers from communities with CAFOs in the vicinity studies several exposures including $PM_{2.5}$

(Schinasi et al., 2011). The participants made twice daily unsupervised lung function measurements, and a small borderline significant effect was seen for a 10µg/m^3 increase in $PM_{2.5}$. However, the participants were not able to adhere to recommended quality by respiratory societies, and the findings are prone to errors, which hampers the inference of the study.

From the Dutch VGO study of health effects on rural dwellers from an area with intensive farming with mixed animals, the first report on lung function is from 2017 (Borlée, Yzermans, Aalders et al., 2017). In this study exposure is estimated either as number of farms in 1000 m buffer or as modelled exposure to NH_3 and PM_{10} during the week preceding the testing for every week during the 9 months of inclusion into the study. In total 2443 adults 20-72 years were included in the analyses mutually adjusted for gender, age, smoking habits, education, being born in the study area, (or stratified) having grown up on a farm. According to mean NH_3 exposure lower FEV_1, FEV_1/FVC and maximum mid-expiratory flow (MMEF) were all significantly lower than predicted. For the number of farms MMEF was significantly lower in persons living in a buffer zone of 1000 m with >25 farms.

In a reanalysis of the VGO study LUR- and dispersion modelling of endotoxin and PM_{10} exposure was used to estimate the exposure in the same population (de Rooij et al., 2019). In this study, it was not possible to show effects of the PM_{10} exposure on lung function. However, a marginal effect of endotoxin was found for FVC. For the symptoms "Wheeze and SOB" and "Daily cough" a strong effect was found related to modelled endotoxin exposure, but only marginal effects were found for PM_{10} exposure. This emphasizes the effect of endotoxin exposure on lung function, as there was no association to PM_{10} for lung function and only marginal effects for symptoms.

From Wisconsin USA a state with almost exclusive dairy operations (90%) Schultz and colleagues selected 1547 rural non farmers from the general health survey (Survey of the Health of Wisconsin (SHOW)) conducted in the period 2008-16 (Schultz et al., 2019). Participants with an acceptable lung function test according to ATS/ERS criteria (1345). The general screening allowed for confounder control for gender, age, BMI, smoking status, education, income and pet ownership. The study found lung function in the close range to nearest CAFO to be negatively affected compared with residents living further away in an exposure response pattern up to 6.8 km FEV1 % predicted 1.6 km vs 3.4 km -7.91%(-14.95, -0.86); 4.8 km -12.03% (-22.7, -1.37); 6.8 km -12.64% (-24.26, -1.01) (table 4 in the online supplement of the article). After 6.4 km the differences were not significant anymore. FEV1/FVC ratio was significantly lower for the residents living closest compared with the people living up to 9.7 km away from nearest CAFO. However, the exposure response also attenuated after 6.4 km. Further FEV_1 is the more robust lung function-measurements in epidemiological studies, when there are no data on end expiratory flow and the handling of the end exhalation.

8.4.1 Susceptible groups

Asthmatic children

Two studies from an agricultural area in Washington State with intensive farming production were performed on asthmatic children. The area of approximately 300 square miles is characterized by a high density of large-scale animal feeding operations, (Loftus, Yost, Sampson, Torres et al., 2015; Loftus, Yost, Sampson, Arias et al., 2015; Loftus et al., 2020). Exposure estimation was based on one local monitoring station. The first study of 58 school aged children (mean age 10 years) explored the effects of $PM_{2.5}$ measured as regional 24-hour average $PM_{2.5}$ measured at a single air monitor located centrally in the study region.

Association between lung function (FEV1%) and IQR increase in 24-hour-average $PM_{2.5}$ measured one day prior (Coefficient (95%CI)) showed a decrease in FEV_1% of −0.9 (−1.8, 0.0) in the 50 children included in the lung function study. When the analysis was stratified according to atopy only, a stronger effect was seen in the 36 atopic children of FEV_1 % of −1.4 (−2.7, −0.2). Confounders included were age, BMI, inhaled corticosteroid use at baseline, and sex.

In the following analysis including 51 children, the exposure was estimated as 24-hour ammonia concentrations. Using a spatially representative approach, a network of 14 devices were deployed outside subject residences (27%) in the 20 * 60 km study region to collect 24 hour samples every six days (Armstrong et al., 2013). The concentrations varied from 0.2 to 238 $\mu g/m^3$, and had a strong correlation with proximity to animal feeding operations.

Association between lung function (FEV1%) and IQR increase with daily ammonia concentration estimated at the address were for FEV_1 a 3.8% decrease (95%CI: 0.2, 7.3) per interquartile increase in 1-day lagged ammonia concentration. When restricting the analyses to the 23 (45%) children living within 1.0 km of an air monitor, FEV1% decreased further to 6.3% (95% CI) 2.3% - 10% 2 days after (lag) exposure. Covariates included in models were temperature and relative humidity (averaged over the week prior, days elapsed in study and seasonality). Also included were subject-specific characteristics potentially associated with asthma: sex, age, atopy, use of inhaled corticosteroids at baseline, body mass index at baseline, and the presence of adult smoker in household.

COPD patients

A recent study from the Dutch VGO program investigated the daily morning and evening lung function in a selected group of non-smoking COPD patients (van Kersen et al., 2020). From the medical examination 213 COPD patients with a good spirometry performance according to ATS/ERS criteria were invited to participate in a 3 month long testing of lung function plus an online questionnaire morning and evening. Exposure was the average daily ambient levels of NH_3 and PM_{10} from the two nearest measuring stations of the Dutch Air Quality Monitoring Network and ambient temperature and relative humidity from the Dutch Meteorological Institute. Participants recorded daily livestock related odour annoyance on a scale from 0-10. COPD was defined as *"(1) a post-bronchodilator (BD) measurement of FEV1/FVC below the lower limit of normal or below 0.7 (Global Initiative for Chronic Obstructive Lung Disease); (2) a pre-BD measurement of FEV1/FVC below 0.7 and wheezing, dyspnea or shortness of breath; (3) self-reported COPD".*

From the associations for air pollution and lung function recordings the study found the FEV1 morning drop for IQR NH_3 (lag 2 days) for > 10% OR (95%CI) 1.05 (1.00-1.13), for > 20% 1.14 (1.05-1.25), and if restriction was made to the 43 participants with POST BD COPD FEV_1/FVC > 20% the risk increased to 1.23 (1.12,1.36). Weaker but significant effects were found for the association to ambient PM_{10} concentrations.

8.4.2 Summary of findings

The included studies are all cross sectional, which inherently is a weakness. However, the studies are designed to target the exposure response functions for exposures, using objective measures of exposure and outcome. Two studies find an effect of ammonia exposure on lung function.

The VGO showed, that FEV_1, FEV_1/FVC and maximum mid-expiratory flow (MMEF) were all significantly lower than predicted. For the number of farms MMEF was significantly lower in persons living in a buffer zone of 1000 m with >25 farms.

For endotoxin exposure a recent analysis of the VGO study using modelling of endotoxin it was possible to establish a link between endotoxin and symptoms as well as lung function, whereas only marginal effects were found for modelled PM_{10} exposure.

For the panel studies it is seen that the effect on lung function is found for NH_3 as well as PM in the patients. Interestingly for both groups the IQR effect of PM seems to be weaker than the NH_3 IQR effect indicating the importance of farming related exposure for the lung response to the local air pollution, in contrast to what were found for symptoms in the same studies.

9 Conclusions

This review has shown, that there is a scarcity of studies shedding light on the association between health and neighborhood exposure to farming operations. Additionally, the included studies are limited to a few specific areas of the Western World leaving out big farming areas like northern Spain, northern Italy and Poland. Also, as for studies of the occupational exposure among farmers, the literature is dominated by cross sectional studies (Sigsgaard et al., 2020). The farm environment is extensively studied and a range of respiratory diseases have been described among the farmers and farm workers, related to the organic dust in the farms (Schenker et al., 1998; Sigsgaard et al., 2020; Omland 2002).

The cross-sectional study design is a problem for risk assessment, as the causal pathway is difficult to assess. There are a few studies following short-term effects in farming exposed susceptible groups. These studies add to the knowledge on the acute effects of the farm related exposures, but they need to be followed up by other studies like intervention trials to proof that the health effects are related to the measured exposures or cohort studies, in order to estimate the long-term effects of the exposures emitted from the farming operations. Intervention studies should be performed as randomized controlled trials and include objective measures of exposure as well as health outcomes. The cohort studies should also include objective measures of exposure as well as health outcomes in order to avoid bias due to the inevitable population knowledge about potential exposure, which may lead to bias, due to the odour they are experiencing. One intervention study in asthmatic children from the same farming area in NW USA as the panels studies emerged from is ongoing and showing a significant reduction in $PM_{2.5}$ in the home air when equipped with two HEPA cleaners one in the child's bedroom and one in the living room. No effect was seen for the NH_3 concentrations (Riederer et al., 2020; Masterson et al., 2020). According to the researchers the health part of the study will be published within the coming 6 months (Catherine Karr, personal communication).

It has not been possible to make a proper risk assessment on the basis of the available studies. This is because the number of studies is low and the vast majority of studies are cross-sectional studies that do not allow a reliable analysis of the causal relationship. Due to the heterogeneity of the included studies, we have refrained from performing a meta-analysis.

Therefore, we have performed best possible synthesis of evidence to arrive at some conclusions, in the following section.

Strong evidence

According to the present review, there is good evidence that NH_3 exposure, as a proxy for farm related exposure, is associated with odour annoyance in the general population. A range of studies have shown that the odour from farm activities are detected by neighbors, and the annoyance is increasing with the concentration of the exposure in a dose dependent manner, using number of farms in the surroundings (Radon et al., 2004; Hooiveld et al., 2015), odour estimation (Boers et al., 2016) or modelled NH_3 as a proxy for farm exposure. (Blanes-Vidal, Bælum, Nadimi et al., 2014).

The studies on Q-fever are encompassing a range of methodologies, all showing an increased risk of Q-fever related to goat farming. This is supported by a meta-analysis consistently finding an increased risk for Q-fever in the vicinity of large goat farms (de Rooij et al., 2017; Post et al., 2019). So even if it is only studied in the Netherlands the evidence is considered to be strong.

Moderate to strong evidence

One well performed panel study on asthmatic children follows school children in NE USA (Loftus, Yost, Sampson, Torres et al., 2015; Loftus, Yost, Sampson, Arias et al., 2015). The study shows a negative effect on lung function (daily FEV_1) by modelled exposure to $PM_{2.5}$ and NH_3 at their home and school address. For an IQR change in $PM_{2.5}$ a decline in FEV_1% of 0.9% was seen dropping further to 1.4% when restricting the analysis to atopic children. For NH_3 the association to IQR was a decline in FEV_1% of 3.8%. In this study, an increased decline of FEV_1 of 6.3% was found when the analysis was restricted to children living within 1.0 km of an air monitor.

A panel study of COPD patients identified by the VGO study followed the patients' daily lung function and symptoms morning and evening for 3 months (van Kersen et al., 2020). Exposure was the average daily ambient levels of NH_3 and PM_{10}. The study found that an IQR increase in ambient NH_3 two days before the lung function measurements were related to an increased risk of a drop in the morning FEV_1. OR for a drop in $FEV_1 > 20\%$ were 1.14 increasing to 1.23 with restriction to the patients with the stricter defined COPD. Weaker but significant effects were found for the association to ambient PM_{10} concentrations.

Interestingly for both asthma and COPD the IQR effect of $PM_{2.5}$ and PM_{10} on FEV_1 seems to be weaker than the NH_3 IQR effect indicating the importance of farm related exposure for the lung response to the local air pollution. This is in contrast to the findings regarding symptoms in the same studies, which are more closely associated to the PM effect.

No other studies confirm the findings above, so the evidence is still only moderate to strong, as it needs confirmation in other well designed studies.

Moderate to weak evidence

Studies of school children have shown increasing symptoms related to the presence of farms in the community (Mirabelli et al., 2006), but this was not found in the NiLS study when using NH_3 as a proxy for farming exposure (Radon et al., 2007).

For adults the results are mixed, and the studies are of cross sectional design. Results are ranging from some effect to an inverse association (a protective effect) of living close to farms (Borlée, Yzermans, Krop et al., 2017), in this study wheezing was increased for COPD patients living near farms.

The VGO study showed a significant increase in current asthma symptoms associated to higher levels of endotoxin and with the PM_{10} level (LUR model) (de Rooij et al., 2019).

A short term follow up in the NiLS study showed that being exposed to high ammonia concentrations ($\geq 19.7\ \mu g/m^3$) at the home address was associated to a decrease in FEV_1 (% predicted) -8.2 (-13.7.-2.7) but no effect on FEV_1/FVC (Borlée, Yzermans, Aalders et al., 2017).

The VGO study showed, that FEV_1, FEV_1 / FVC and maximum mid-expiratory flow (MMEF) were all significantly lower than predicted in the people living in the intensive farming area. Using the number of farms in the analysis MMEF was significantly lower in persons living in a buffer zone of 1000 m with >25 farms.

In Wisconsin (Schultz et al., 2019) found lung function in the close range to nearest CAFO to be negatively affected compared with residents living further away in an exposure response pattern up to 6.8 km FEV_1 % predicted at 1.6 km vs 3.4 km, 4.8 km and 6.8 km to be -8%, -12% and -13%, respectively.

These results point to a potential role of emitted bacterial agents such as endotoxins from Gram-negative bacteria.

All these studies are cross sectional and therefore the evidence is weak, and needs replication in independent additional studies. Also, more studies with a stronger design are needed to fully elucidate these associations.

Weak evidence

The cross sectional studies are giving of mixed results for the association between symptoms and odour. Due to the inherent detection of odour by the olfactory system, it is almost impossible to disentangle the effects directly related to the odour and the effects mediated through annoyance. One good study using a mediation analysis found a direct effect of NH_3 on respiratory symptoms as well as an indirect effect mediated via odour annoyance (Blanes-Vidal, Baelum, Schwartz et al., 2014). However, the evidence is considered weak since this is the only study with this type of information.

For the panel studies with susceptible populations no associations are seen between ammonia exposure and respiratory symptoms neither in the asthmatic children nor in the COPD patients. However, a clear effect of weekly $PM_{2.5}$ exposure is seen among the asthmatic children. This is making the inference difficult, since the suspected marker of local farm exposure ammonia is not associated. At the same time the fine particulates being a mix of local and long transport particles and related to farming as well as traffic is showing a significant association to symptomatology in the asthmatic children. However, it is impossible to distinguish exposure related to farms and to traffic associated PM.

The Danish study used modelled ammonia exposure at the addresses and psychosocial, respiratory symptoms and behavioral changes. The study found in mediation analyses a possible direct effect of the NH_3 on respiratory effects. The authors state that these effects could be explained either because NH_3 is a marker of a general exposure to organic pollutants from farming e.g. endotoxin, or it might be an effect of reverse causation i.e. exposure → symptoms → annoyance.

In the studies of allergy in persons living close to farms only the recent VGO study finds an effect of farming exposure on the lower allergy rates. However, it has been seen in studies spanning farmers, non-farming rural dwellers before, and is likely a corroboration of a common trend in allergy varying from urban to rural to farm environment.

Regarding pneumonia, the observed associations between poultry in the neighborhood and pneumonia need more attention, however right now the evidence is still considered weak.

Insufficient evide 4nce

The effect of CAFOs on general morbidity and mortality has not been studied enough, and so far the studies are lacking important information on important confounders, hampering the ability to draw conclusions.

9.2 Final statement

All in all the review of the current evidence points to annoyance in the general population due to farming exposure in the ambient air, in a dose dependent manner.

Further negative effects on health are found in susceptible groups like asthmatic especially children and COPD patients.

More studies from more countries are needed to confirm the findings in the susceptible groups, and there is an urgent need for follow up studies of the general population living in the neighborhood of intensive farming areas.

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Appendix 1 References

Tabel 1. Original contributions CAFOs

#	Title	Authors	Journal/Book	Year
1	Morbidity Rates in an Area with High Livestock Density: A Registry-Based Study Including Different Groups of Patients with Respiratory Health Problems	Baliatsas C, Döckers M, Smit L, Heederik D, Yzermans J.	Int J Environ Res Public Health	2020
2	Acute respiratory effects of livestock-related air pollution in a panel of COPDpatients	van Kersen, Oldenwening , Aalders, Bloemsma, Borlée, Heederik, Smit	Environ Int	2020
3	Patients with overlapping diagnoses of asthma and COPD: is livestock exposure a risk factor for comorbidity and coexisting symptoms and infections?	Baliatsas C, Smit LAM, Döckers MLA, van Dijk CE, Heederik D, Yzermans CJ.	BMC Pulm Med	2019
4	Endotoxin and particulate matter emitted by livestock farms and respiratory health effects in neighboring residents	de Rooij MMT, Smit LAM, Erbrink HJ, Hagenaars TJ, Hoek G, Ogink NWM, Winkel A, Heederik DJJ, Wouters IM.	Environ Int	2019
5	Residential proximity to concentrated animal feeding operations and allergic and respiratory disease	Schultz AA, Peppard P, Gangnon RE, Malecki KMC.	Environ Int	2019
6	Residential proximity to livestock farms is associated with a lower prevalence of atopy	Borlée F, Yzermans CJ, Krop EJM, Maassen CBM, Schellevis FG, Heederik DJJ, Smit LAM.	Occup Environ Med	2018
7	Associations between pneumonia and residential distance to livestock farms over a five-year period in a large population-based study	Kalkowska DA, Boender GJ, Smit LAM, Baliatsas C, Yzermans J, Heederik DJJ, Hagenaars TJ.	PLoS One	2018
8	Comorbidity and coexisting symptoms and infections presented in general practice by COPD patients: Does livestock density in the residential environment play a role?	Baliatsas C, Borlée F, van Dijk CE, van der Star B, Zock JP, Smit LAM, Spreeuwenberg P, Heederik D, Yzermans CJ.	Int J Hyg Environ Health	2017
9	Mortality and Health Outcomes in North Carolina Communities Located in Close Proximity to Hog Concentrated Animal Feeding Operations	Kravchenko, J., S. H. Rhew, I. Akushevich, P. Agarwal, and H. K. Lyerly.	N C Med J	2018
10	Air Pollution from Livestock Farms Is Associated with Airway Obstruction in Neighboring Residents	Borlée F, Yzermans CJ, Aalders B, Rooijackers J, Krop E, Maassen CBM, Schellevis F, Brunekreef B, Heederik D, Smit LAM.	Am J Respir Crit Care Med	2017
11	Spirometry, questionnaire and electronic medical record based COPD in a population survey: Comparing prevalence, level of agreement and associations with potential risk factors	Borlée F, Yzermans CJ, Krop E, Aalders B, Rooijackers J, Zock JP, van Dijk CE, Maassen CB, Schellevis F, Heederik D, Smit LA.	PLoS One	2017
12	Livestock-associated risk factors for pneumonia in an area of intensive animal farming in the Netherlands	Freidl GS, Spruijt IT, Borlée F, Smit LA, van Gageldonk-Lafeber AB, Heederik DJ, Yzermans J, van Dijk CE, Maassen CB, van der Hoek W.	PLoS One	2017
13	Proximity to Industrial Food Animal Production and Asthma Exacerbations in Pennsylvania, 2005-2012	Rasmussen SG, Casey JA, Bandeen-Roche K, Schwartz BS.	Int J Environ Res Public Health	2017
14	Impacts of Intensive Livestock Production on Human Health in Densely Populated Regions	Smit LAM, Heederik D.	Geohealth	2017
15	Increased risk of pneumonia in residents living near poultry farms: does the upper respiratory tract microbiota play a role?	Smit LAM, Boender GJ, de Steenhuijsen Piters WAA, Hagenaars TJ, Huijskens EGW, Rossen JWA, Koopmans M, Nodelijk G, Sanders EAM, Yzermans J, Bogaert D, Heederik D.	Pneumonia (Nathan)	2017

16	Health conditions in rural areas with high livestock density: Analysis of seven consecutive years	van Dijk CE, Zock JP, Baliatsas C, Smit LAM, Borlée F, Spreeuwenberg P, Heederik D, Yzermans CJ.	Environ Pollut	2017
17	The relation between modeled odor exposure from livestock farming and odor annoyance among neighboring residents	Boers D, Geelen L, Erbrink H, Smit LA, Heederik D, Hooiveld M, Yzermans CJ, Huijbregts M, Wouters IM.	Int Arch Occup Environ Health	2016
18	Doctor-diagnosed health problems in a region with a high density of concentrated animal feeding operations: a cross-sectional study	Hooiveld M, Smit LAM, van der Sman-de Beer F, Wouters IM, van Dijk CE, Spreeuwenberg P, Heederik DJJ, Yzermans CJ.	Environ Health	2016
19	Associations between proximity to livestock farms, primary health care visits and self-reported symptoms	van Dijk CE, Smit LA, Hooiveld M, Zock JP, Wouters IM, Heederik DJ, Yzermans CJ.	BMC Fam Pract	2016
20	Risk of exacerbations in COPD and asthma patients living in the neighbourhood of livestock farms: Observational study using longitudinal data	van Dijk CE, Garcia-Aymerich J, Carsin AE, Smit LA, Borlée F, Heederik DJ, Donker GA, Yzermans CJ, Zock JP.	Int J Hyg Environ Health	2016
21	Increased respiratory symptoms in COPD patients living in the vicinity of livestock farms	Borlée F, Yzermans CJ, van Dijk CE, Heederik D, Smit LA.	Eur Respir J	2015
22	Odour annoyance in the neighbourhood of livestock farming - perceived health and health care seeking behaviour	Hooiveld M, van Dijk C, van der Sman-de Beer F, Smit LA, Vogelaar M, Wouters IM, Heederik DJ, Yzermans CJ.	Ann Agric Environ Med	2015
23	Air pollution from livestock farms, and asthma, allergic rhinitis and COPD among neighbouring residents	Smit LA, Hooiveld M, van der Sman-de Beer F, Opstal-van Winden AW, Beekhuizen J, Wouters IM, Yzermans CJ, Heederik D.	Occup Environ Med	2014
24	Odors from sewage sludge and livestock: associations with self-reported health	Wing S, Lowman A, Keil A, Marshall SW.	Public Health Rep	2014
25	Effects on pulmonary health of neighboring residents of concentrated animal feeding operations: exposure assessed using optimized estimation technique	Schulze A, Römmelt H, Ehrenstein V, van Strien R, Praml G, Köchenhoff H, Nowak D, Radon K.	Arch Environ Occup Health	2011
26	Air pollution, lung function, and physical symptoms in communities near concentrated Swine feeding operations.	Schinasi L, Horton RA, Guidry VT, Wing S, Marshall SW, Morland KB.	Epidemiology	2011
27	Environmental exposure to confined animal feeding operations and respiratory health of neighboring residents	Radon K, Schulze A, Ehrenstein V, van Strien RT, Praml G, Nowak D.	Epidemiology	2007
28	[Associations between bioaerosols coming from livestock facilities and asthmatic symptoms in children]	Hoopmann M, Hehl O, Neisel F, Werfel T.	Gesundheitswesen	2006
29	Asthma Symptoms Among Adolescents Who Attend Public Schools That Are Located Near Confined Swine Feeding Operations	Mirabelli MC, Wing S, Marshall SW, Wilcosky TC.	EHP	2006
30	[Prevalence of respiratory symptoms and diseases in neighbours of large-scale farming in Northern Germany]	Radon K, Schulze A, Strien Rv, Ehrenstein V, Praml G, Nowak D.	Pneumologie	2005
31	Health effects from breathing air near CAFOs for feeder cattle or hogs	Von Essen SG, Auvermann BW.	J Agromedicine	2005
32	Odour influence on well-being and health with specific focus on animal production emissions	Nimmermark S.	Ann Agric Environ Med	2004
33	Livestock odours and quality of life of neighbouring residents	Radon K, Peters A, Praml G, Ehrenstein V, Schulze A, Hehl O, Nowak D.	Ann Agric Environ Med	2004
34	Intensive livestock operations, health, and quality of life among eastern North Carolina residents	Wing S, Wolf S.	Environ Health Perspect	2000
35	[MORBUS: the Sentinel Practice Network. Report on a study in South Oldenbury]	Schlaud M, Salje A, Nischan P, Behrendt W, Gröger J, Schäfer T, Schwartz FW.	Dtsch Tierarztl Wochenschr	1998

Table 2. Other studies not included as main articles

#	Title	Authors	Journal/Book	Year
	Exposure studies			
1	The home air in agriculture pediatric intervention (HAPI) trial: Rationale and methods	Masterson EE, Younglove LB, Perez A, Torres E, Krenz JE, Tchong French MI, Riederer AM, Sampson PD, Metwali N, Min E, Jansen KL, Aisenberg G, Babadi RS, Farquhar SA, Thorne PS, Karr CJ.	Contemp Clin Trials	2020
2	Anhydrous Ammonia Chemical Release - Lake County, Illinois, April 2019	Rispens JR, Jones SA, Clemmons NS, Ahmed S, Harduar-Morano L, Johnson MD, Edge C 3rd, Vyas A, Bourgikos E, Orr MF.	MMWR Morb Mortal Wkly Rep	2020
3	Spatial and temporal variation in endotoxin and PM10 concentrations in ambient air in a livestock dense area	de Rooij MM, Heederik DJ, Borlée F, Hoek G, Wouters IM.	Environ Res	2017
4	Livestock farming and atmospheric emissions	Zicari G, Soardo V, Rivetti D, Cerrato E, Russo D.	Ig Sanita Pubbl	2013
5	Community exposure following a drip-application of chloropicrin	Barry T, Oriel M, Verder-Carlos M, Mehler L, Edmiston S, O'Malley M.	J Agromedicine	2010
6	Air pollution and odor in communities near industrial swine operations	Wing, S., Horton, R. A., Marshall, S. W., Thu, K. Tajik, M., Schinasi, L., Schiffman, S. S.	Environ Health Perspect	2008
7	Monitoring and modeling of emissions from concentrated animal feeding operations: overview of methods	Bunton B, O'shaughnessy P, Fitzsimmons S, Gering J, Hoff S, Lyngbye M, Thorne PS, Wasson J, Werner M.	Environ Health Perspect	2007
	Other non CAFO related studies			
1	Residential proximity to agricultural fumigant use and respiratory health in 7-year old children	Gunier RB, Raanan R, Castorina R, Holland NT, Harley KG, Balmes JR, Fouquette L, Eskenazi B, Bradman A.	Environ Res	2018
2	Elemental Sulfur Use and Associations with Pediatric Lung Function and Respiratory Symptoms in an Agricultural Community (California, USA)	Raanan R, Gunier RB, Balmes JR, Beltran AJ, Harley KG, Bradman A, Eskenazi B.	Environ Health Perspect	2017
	Other			
1	Health risks associated with livestock farms	Health Council of the Netherlands	I-1008/11/ES/db/812-D	2012
2	Ammonia, ammonium, and the risk of asthma: A register-based case–control study in Danish children	Holst, G. Thygesen, M. Pedersen, Peel CB, Jørgen B, Christensen, JH.; Bønløkke, JH.; Hertel, O; Sigsgaard, T	Environmental Epidemiology	2018
3	Air pollution and family related determinants of asthma onset and persistent wheezing in children: nationwide case-control study.	Holst GJ, Pedersen CB, Thygesen M, Brandt J, Geels C, Bønløkke JH, Sigsgaard T.	BMJ	2020
4*	The antimicrobial resistome in relation to antimicrobial use and biosecurity in pig farming, a metagenome-wide association study in nine European countries.	Van Gompel L, Luiken REC, Sarrazin S, Munk P, Knudsen BE, Hansen RB, Bossers A, Aarestrup FM, Dewulf J, Wagenaar JA, Mevius DJ, Schmitt H, Heederik DJJ, Dorado-García A, Smit LAM	J Antimicrob Chemother	2019
5*	Evaluation of Patients with Community-Acquired Pneumonia Caused by Zoonotic Pathogens in an Area with a High Density of Animal Farms	Huijskens EG, Smit LA, Rossen JW, Heederik D, Koopmans M.	Zoonoses Public Health	2016

* Zoonoses and antibiotic resistance not included

Table 3. Systematic and other reviews

#	Title	Authors	Journal/Book	Year
1	Respiratory health effects of exposure to low levels of airborne endotoxin - a systematic review	Farokhi A, Heederik D, Smit LAM.	Environ Health	2018
2	A systematic review of the public health risks of bio-aerosols from intensive farming.	Douglas P, Robertson S, Gay R, Hansell AL, Gant TW	Int. J of Hygiene and Env Health	2018
3	Updated systematic review: associations between proximity to animal feeding operations and health of individuals in nearby communities.	O'Connor AM, Auvermann BW, Dzikamunhenga RS, Glanville JM, Higgins JPT, Kirychuk SP, Sargeant JM, Totton SC, Wood H, Von Essen SG.	Syst Rev.	2017
3a	O'Connor et al. systematic review regarding animal feeding operations and public health: critical flaws may compromise conclusions	Nachman KE, Lam J, Schinasi LH, Smith TC, Feingold BJ, Casey JA.	Syst Rev.	2017
3b	Authors' response to comments from Nachman KE et al.	O'Connor AM, Auvermann BW, Dzikamunhenga RS, Glanville JM, Higgins JPT, Kirychuk SP, Sargeant JM, Totton SC, Wood H, Von Essen SG.	Syst Rev.	2017
4	Industrial food animal production and community health.	Casey JA, Kim BF, Larsen J, Price LB, Nachman KE.	Curr Environ Health Rep.	2015
5	The public health impacts of concentrated animal feeding operations on local communities	Greger M, Koneswaran G.	Fam Community Health	2010
6	Environmental health effects of concentrated animal feeding operations: implications for nurses	McElroy KG.	Nurs Adm Q	2010
7	Community and environmental health effects of concentrated animal feeding operations	Kirkhorn SR.	Minn Med	2002
8	Public health concerns for neighbors of large-scale swine production operations	Thu KM.	J Agric Saf Health	2002
9	The concentration of swine production. Effects on swine health, productivity, human health, and the environment	Donham KJ.	Vet Clin North Am Food Anim Pract	2000
10	[Protection of residents in the vicinity of intensive livestock units from possible health risks]	Möhle R	Dtsch Tierarztl Wochenschr	1998
11	Livestock odors: implications for human health and well-being	Schiffman SS.	J Anim Sci	1998

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Review of the scientific evidence of air pollution causing health effects in people living in the vicinity of concentrated animal feeding operations (CAFOs)

Gennemgang af de eksisterende videnskabelige undersøgelser af helbredseffekter af luftforurening hos naboer til store husdyrbrug

This report reviews the literature concerning health effects of exposure to emissions from animal husbandry and health effects in people living in the vicinity of concentrated animal feeding operations. This review has shown, that there is a scarcity of studies shedding light on the association between health and neighborhood exposure to farming operations. There are a few studies on short-term effects in farming exposed susceptible groups. These studies add to the knowledge on the acute effects of the farm related exposures, but they need to be followed up by cohort studies in or-der to estimate the long-term effects of the exposures emitted from the farming operations.

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