NATUR VÅRDS VERKET

Miljöforskningsnämnden
Ansökan om projektbidrag inom Naturvårdsverkets forskningsprogram

Forskningsprogram
SNAP X **REPROSAFE** **FLIPP** Inriktning: Ekonomiska styrmedel
Inriktning: Informationssystem och indikatorer IPP

Projekttitel (svensk):
Sjukdomsutlösande effekter av luftföroreningar och deras interaktion vid i samhället vanliga infektioner

Projekttitel (engelsk):
Infectious disease-promoting effects of air-borne environmental pollutants

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Sammanfattning på **svenska** strukturerad enligt följande: 1) Projektets betydelse för programmet 2) Miljörelevans och förväntad betydelse för miljöpolitiken 3) Mål och hypotes 4) Metodik och genomförande 5) Kommunikationsinsatser i relation till programmet:

Ad 1). Gällande gränsvärden för miljöföroreningar är baserade på vad som ur hälsosynpunkt visats acceptabelt för den i övrigt friska individen. Senare års forskning ger emellertid stöd för hypotesen att upprepade infektioner minskar toleransen för många miljöföroreningar med ökade hälsorisker på sikt. Under en infektion ökar upptaget från tarmen av många miljöföroreningar samt distribueras dessa till och ansamlas i vitala organ i kroppen istället för att utsöndras. Kunskapen hittills begränsas till upptag från tarmen vid infektioner som primärt angriper magtarmkanalen. Denna ansökan avser likartade studier vad gäller studier av luftburna miljöföroreningar och luftburna infektioner, där denna typ av kunskap saknas. Luftburna infektioner är de vanligaste infektionerna, ej minst hos barn, och alla människor utsätts för ett stort antal av sådana under livet.

Ad 2). Vi tror att samverkanseffekter av luftföroreningar och i samhället vanliga infektioner är av central betydelse för många individers hälsa och därför behöver beaktas i framtida riskvärdering. Med en ökad kunskap om sådana interaktioner kan känsliga individer och populationer (t.ex. yrkesexponerade individer med frekventa infektioner) identifieras och ges rekommendationer i syfte att motverka ett försämrat hälsostatus på sikt.

Ad 3). Hypotesen är att luftburna miljöföroreningar (liksom tidigare visat för föroreningar i mat/dryck) har en ökad toxicitet, innebärande ökade hälsorisker, hos individer som bär på en infektion. Vidare tror vi att luftburna infektioner med sin smittväg och inflammatoriska skador i luftvägarna, för vissa föroreningar, kan resultera i andra toxiska effekter än de man ser vid infektioner i magtarmkanalen. Målet är att experimentellt studera dessa förhållanden, eftersom kunskap här saknas.

Ad 4). Vi har stor vana vid experimentella toxicitets- och infektionsstudier på små gnagare. Vi har visat att lågdosexponering för miljögifter (kadmium, nickel, kvicksilver, dioxin) via födan, dels kan försvåra förloppet av vanliga mag-tarmvirusinfektioner, dels leda till att dessa ämnen upptas i större mängd och omfördelas i kroppen ledande till en ökad/förändrad toxicitet. Syftet med studierna är att undersöka hur upptag/distribution i kroppen och den toxiska effekten av olika luftburna miljöföroreningar påverkas under akuta luftvägsinfektioner orsakade av virus (influensa) och vid mera långdragna infektioner orsakade av bakterier (*Chlamydia pneumoniae*). Vidare är syftet att undersöka om tillförsel av essentiella spårämnen som zink, järn och selen kan interagera med potentiellt toxiska metaller och därmed begränsa de skadliga effekterna som ses vid infektion. Det finns visst vetenskapligt stöd för att dessa essentiella spårämnen kan minska upptag i kroppen och i organ av toxiska metaller och därmed ge en skyddande effekt. Vi kommer att använda olika immunologiska metoder för mätning av påverkan på immunfunktionen/infektionsförsvaret, polymeraskedjereaktionen (PCR) för påvisande av smittämnet, m.fl. metoder.

Ad 5). Resultat kommer att publiceras i internationella tidskrifter med "editorial board".

	År 2004	År 2005
Summa sökta medel per år i kr:	1161.000	1178.000

Miljöforskningsnämnden
Ansökan om projektbidrag inom Naturvårdsverkets forskningsprogram

Sökta projektmedel fördelade på kostnadsslag	År 2004 (kr)	År 2005 (kr)
Personalkostnad inkl. soc. avgifter * Biomedicinsk analytikerlön/doktorand 18.000 kr/mån + LKP 51.5 % (9.270 kr) = 27.270 kr/mån	327.000	340.000
Övriga omkostn exkl moms (förbrukningsmtrl, analyser, resor etc)**		
Utrustning för inhalationsstudier	300.000	75.000
Reagens för PCR, cytokiner, virus/bakteriedetektion, biokemiska analyser	100.000	250.000
Metallanalyser (ICP-MS, mikrosond, isotoper)	50.000	55.000
Djur och djurhållningskostnader vid infektionsavdelning	100.000	150.000
Resa, transport av vävnad för metall-distributionsstudier (Singapore, mikrosond)	30.000	50.000
Delsumma av ovanstående poster:	907.000	920.000
Förvaltningspåslag: Högskolemoms 8 % + Förvaltningsavgift. 20 % = ...28 %	254.000	258.000
Totalsumma per år: (införs sid. 1):	1161.000	1178.000

*) Specificera namn, tjänst **) Specificera

Samtliga övriga miljörelaterade projekt för vilka de sökande har beviljats anslag eller söker anslag för 2004-2006. OBS Även EU-finansiering.

Projekttitel	Finansiär	Tidsperiod	Sökt kr	Beviljat kr

Miljörelaterade projekt för vilka sökande har beviljats anslag för 2000-2003
OBS Även EU-finansiering

Projekttitel	Finansiär	Tidsperiod	Beviljat Kr

Datum och sökandes underskrift, vilken samtidigt ger Naturvårdsverket tillåtelse att publicera sökandes namn på sin webbplats:	Datum och underskrift av prefekt eller motsvarande med namnförtydligande: Göran Friman / Professor

Ansökan skall bestå av detta formulär jämte högst sex sidor lång projektbeskrivning på **engelska** (strukturerad som den svenska sammanfattningen samt en redovisning av kunskapsläget). Referenser till egna publikationer ges med sifferhänvisning till CV. Andra referenser ges i löpande text. Sökandes och eventuell medsökandes CV får omfatta högst två sidor. Inga bilagor kommer att beaktas vid bedömningen. Ansökan (max 10 A4-sidor, 12 punkters teckenstorlek) skall inlämnas i **original + 15 kopior samt elektroniskt** till ansok@naturvardsverket.se. Häfta ihop ansökan och använd hålat papper. Ansökan skall ha inkommit senast den 15 oktober 2003 till Naturvårdsverket, Forskningssekretariatet, 106 48 STOCKHOLM.

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Uppsala 2003-10-14

Infectious disease-promoting effects of air-borne environmental pollutants

The project's role and significance for the programme

There is a wide spread low dose repeated exposure of the population to a variety of chemical pollutants of environmental or occupational origin. It has long been known that certain environmental pollutants, such as cadmium (Cd) and mercury (Hg), may cause disease in animals and man as a result of high dose-exposure (Elinder and Järup 1996; Järup et al 1998; Lawrence 1985). Even low-dose exposure in animals has sometimes been shown to promote clinical symptoms and disease, especially if continued over extended periods of time. The adverse effects of these and other pollutants seem to be exercised by toxic effects on the immune defence (Lawrence 1985) that may increase the individual's proneness to develop severe disease caused by exogenic factors, such as microorganisms, i.e. viruses (Ellermann-Eriksen et al 1994;Gainer 1977;12,13,17,22). It has thus been suggested that PCB and TCDD related compounds are the cause of the high mortality found in morbillivirus-infected mammals in waters polluted with these compounds (Borrell et al 1996). It is apparent from a host of clinical studies that suppression of the immune system is characteristically associated with the increased susceptibility to different infectious diseases.

There are common microorganisms, to which all humans are repeatedly exposed during their life-time, such as gastrointestinal infections caused by the coxsackieviruses and respiratory viruses, including the influenzaviruses and the respiratory bacteria *Chlamydia pneumoniae* (C.p). Generally, air-borne infections are among the most common of all infections and each individual suffers a great number of air-borne infections during life. For example, approximately 70% of elderly people have antibodies to C.p. as a marker of previous infection with that bacterium, which is spread worldwide with cyclic variations over time (Nyström-Rosander 2002). Although the above-mentioned microorganisms cause only mild-to-moderate symptoms in a majority of cases, they sometimes give rise to aggravated disease as well as complications, such as pneumonia, myocarditis, pancreatitis and meningoencephalitis and even atherosclerotic lesions, depending on type of organism (Woodruff 1980; 14,22,28). The murine models of coxsackievirus B3 (CB3), influenza and C.p. have a well-described pathogenesis that closely mimics the pathology of these diseases in humans (Woodruff 1980; Wynne and Braunwald 1980; Yang et al 1993; 4,5,14).

The host's normal defence to infection (the acute-phase response) includes increased synthesis of metal binding proteins and a concomitant flux of trace elements between blood and tissues in order to supply substrate for an efficient immune cell function (25,26,30). Zinc (Zn) is essential for well-functioning immune cells (Driessen and Rink 1995; 16), which is in line with several reports showing that depletion of Zn by chelation can trigger apoptosis in virally transformed cells (Fernandez-Pol et al 2001). However, toxic metals (Hg, Cd), can adversely compete with essential trace elements ((Zn, iron (Fe), copper (Cu), selenium (Se)), in the healthy individual (Goyer 1997; 12) and also affect apoptosis in normal cells (Shen et al 2001). We have observed in infection that the trace element balance in target organs of the infection is changed (19,20,25,26,27,28) and that Hg exposure seems to result in prolonged virus persistence compatible with the development of chronic disease (22). It is unknown by which mechanisms toxic metals compete with essential elements and affect the immune response, virulence and apoptosis in the infected host.

During coxsackievirus infections and the associated immune activation, we have shown that the gastrointestinal uptake of environmental pollutants (Ni, Cd, Hg), even at those low doses normally found in food, is increased and their target organ distribution changed (9,13,21,22). In experimental anomals this has been shown to result in aggravated disease, including complications (14,15,17,25). For influensa and herpes simplex virus infections limited but similar information has been reported (Burleson et al 1996; Ellermann-Eriksen et al 1994). Administration of Cd prior to the infection has also been shown to increase the susceptibility of mice to infections by cytomegalovirus (CMV) (Daniels et al 1987), Herpes simplex virus (HSV) (Thomas et al 1985), encephalomyocarditis virus (EMCV), semliki forest virus (SFV) and Venezuelan Equine Encephalitis virus (VEEV) (Seth et al 2003). Moreover, recently Fawl and colleagues reported reactivation of HSV after Cd exposure (Fawl et al 1996).

We have also shown that infection down-regulates the detoxifying system (P-450) and greatly (several-fold) induces metallothionein synthesis (24,30). Metallothionein gene expression is increased in peripheral lymphocytes of Cd exposed workers (Lu et al 2000) and toxicokinetics and biochemistry of essential and toxic metals are often related to metallothionein (Nordberg and Nordberg 2000). Infections induce cytokine responses (17) and cytokines have been shown to upregulate metallothionein gene expression (Borghesi et al 1996). Metallothionein binds essential trace metals such as Cu and Zn, but can also bind toxic metals such as Cd and Hg. Thus, an infection-induced increase in metallothionein synthesis in immune cells, such as lymphocytes, and in target organs of many infections, such as the lungs, brain, liver and kidneys, resulting in increased uptake and accumulation of toxic metals, could subsequenly be detrimental to the host.

It would seem, for two reasons, that the above issues are particularly relevant to the fast-growing fetus, new-born child and children in general. Children have a higher metabolic turnover and are more frequently exposed to viruses and thus more frequently infected by viruses than adults, possibly resulting in both a more rapid and a more continuous accumulation of toxic pollutants in target organs. In addition, if the mother is exposed to low doses of dietary Hg there is a placental and lactational transfer of Hg that adversely affects the developing immune system in the pups (8). It is also well-known that pharmacologically active compounds show age-dependent changes in uptake and distribution in the brain, with different patterns in young as compared to older animals (Eriksson 1997; Stålhandske and Slanina 1970). It has recently also been shown that the perinatal brain development is vulnerable to various toxic agents, such as DDT and PCB, even at low doses (Eriksson 1997). Furthermore, such exposure to low-doses early in life can subsequently lead to increased susceptibility in the adult even to other neurotoxic agents (Eriksson et al 2000). In addition, we have shown that previously accumulated pollutants (TCDD) become redistributed from its principal target organ (fat tissue and liver) into the brain during coxsackievirus infection (21). Moreover, inflammatory cytokines, such as those induced in viral infections, have been shown to alter the blood brain barrier permeability which may facilitate the entry of chemical compounds in brain tissue (Seth et al 2003).

These adverse interactions between the infectious process and toxic pollutants seem to have a multifactorial explanation; in brief, firstly the immune system becomes compromized by the pollutants and functions less efficiently (7), secondly, the uptake of potentially toxic metals is increased resulting in disturbed balance of essential trace metals as well in increased target organ toxicity (11,14), and thirdly, toxic pollutants may disturb the balance of essential trace elements in a way that allows the microorganism to mutate into more aggressive variants (Al-Younes et al 2001; Beck et al 1994; Takeoshi et al 1994; Vartainen et al 1999). These new issues need to be further studied even for different microorganisms, such as air-borne viruses and bacteria, as well as for air-borne environmental pollutants. It is well-known, in the healthy individual, that the uptake of some chemical compounds, such as Cd, is higher from the respiratory tract than from the gastrointestinal tract. Whether an infection-associated increase in uptake and changes in immune function and target organ distribution occur after inhalation exposure, is however unknown. Neither is it known whether infections located in the respiratory tract give rise to a different chain of events regarding pollutant uptake and distribution.

Environmental relevance and and expected significance for environmental policy

Humans are constantly exposed to infections, and concomitant exposition to various environmental pollutants occur frequently. Potentially hazardous interactions have been shown to occur for some viruses and can be expected even for other microorganisms. Hitherto published studies are limited to a few important environmental pollutants (Ni, Cd, Hg, TCDD) mainly studied in the common coxackie virus infection that is transmitted through the upper and lower gastrointestinal tract. Therefore, further studies will have to be expanded to include these and other pollutants in other common infections with a different route of transmission such as influenza and C.p., which are transmitted through inhalation. Even though the interpretation of results in animals to humans may sometimes be difficult, a firm basis of knowledge of the underlying disease-promoting mechanisms of the microorganism-pollutant interactions and resulting toxicity enhancement is needed before further actions could be taken.

It is anticipated that these new data will be a valuable contribution in future risk assessment in order to identify populations at special exposure risk regarding health and disease status. Several options of intervention may be considered, such as reducing environmental pollution, either generally or specifically aimed at hazardous toxicants and/or populations. Restrictions may be needed for special groups at risk, such as for individuals living or working in highly polluted areas, as well as for children, pregnant women and people showing increased incidence or longer periods of infectious episodes.

Objective and hypothesis

The widespread environmental contamination of several metals, including Cd, Hg and Ni, and other chemical compounds, including organohalogen compounds, in the face of the fact that humans normally suffer multiple infections during the lifetime which may aggravate the toxic effects are indicative that further studies are important to understand their influence on human health. The knowledge of infection-pollutant interactions is currently essentially limited to orally/intestinally administered pollutants in gastrointestinal infections. Therefore, new infection studies should include air-borne pollutant as well as respiratory infections.

In acute coxsackie virus infection, transmitted by the gastrointestinal route, orally administered environmental pollutants seem to have its own specific organ and tissue distribution in the body, as well as its own disease-promoting action. Thus, in general the infection potentiates the adverse effects of the specific pollutant. In brief, during coxsackievirus infection, the gastrointestinal uptake of some environmental pollutants (e.g. Hg, Cd, Ni and TCDD) is increased, for Cd even dose-dependently (19). In addition, their locations shift from their "normal storing organs and tissues" to vital organs, such as the heart, brain, and kidneys resulting in potentially harmful levels. Also, the infection takes a more severe course in pollutant-exposed animals than in nonexposed infected animals and immune parameters indicate that immune function is less efficient in exposed animals (7,8,10,14,17). Thus, because all individuals suffer a great number of various infections during the lifetime, these effects should be taken into account in risk assessments. However, distribution studies in infections have not been published at air-borne exposure of pollutants during infection. Neither has uptake nor target organ distribution of pollutants during respiratory viral infections, such as influenza and common respiratory bacterial infections, such as *Chlamydia pneumoniae* (C.p.), been studied. There are reasons to believe that the pollutant distribution to target organs may be different with a different part of entry of the pollutant, as well as of the infection.

One objective of the present application is to study, in common human viral and bacterial infections, whether and to what extent the above results, hitherto published, are relevant also to air-borne pollutants, acquired by aerosol through the respiratory tract. Because one important port of entry of aerosol pollutants is the nasal epithelium, which is anatomically close to the brain, tissue analysis of uptake and distribution in the brain is going to be included in the studies. In addition to the gastrointestinal coxsackievirus infection, used in our previous studies on environmental pollutants, we intend to use both a viral (influenza) and a bacterial (C.p.) infection, acquired through the respiratory tract, primarily the nasal and pharyngeal epithelium. We have previously used influenza virus in other studies (1,2) and we have experience of C.p. from human tissue specimens (28). Because each environmental pollutant tends to have its own pattern of distribution in the body they have to be individually studied. As a first step we will continue our studies using the metals Cd, Ni and Hg, where we have experience from coxsackievirus infection.

Another objective is to study environmental pollutants in experimental chronic disease models (various coxsackieviruses, C.p.), which are available in our laboratory. Low-dose exposure, including aerosol exposure, to pollutants over extended periods of time may adversely influence the susceptibility and the progression of chronic infection-associated diseases.

A third objective is to study whether supplementation of essential trace metals, such as Zn, Fe and Se, can compete with the uptake and distribution of non-essential and potentially toxic metals, such as Cd, and possibly limit the toxicity and the disease. Our previous studies in humans and animals have shown market and often dramatic changes in several trace elements in blood and tissues during both viral and bacterial infections (23,26-30). Thus, there is reason to believe that an interaction exists between metal pollutants, such as Cd, and certain essential trace metals, such as Zn, Cu and Fe, the biological importance of which may be exaggerated during infection, such as causing changed virulence, pathogenesis and infection-induced increase in toxicity of environmental pollutants.

It may be expected that the results generated in the proposed studies will improve future risk assessment and help identifying populations at special risk.

Methods and implementation

The murine model of the gastrointestinal coxsackievirus B3 (CB3) and the respiratory influenza and C.p. infection will be used. This is an area where we have considerable experience (refs. see CV). Organ complications (e.g. myocarditis, pancreatitis and meningoencephalitis) and associated lesions (inflammation, necrosis, lipid accumulation) will be evaluated by traditional histopathological techniques.

We will take advantage of established, as well as new techniques, for the study of immune cell subpopulations and their function, induction of metal binding proteins, histopathological and immunopathological lesions, uptake and tissue distribution of pollutants after both CB3, influenza and C.p. infections, as well as nucleic acid hybridisation for the detection of microorganisms and nucleotide sequencing for their mutations (refs. see CV). The work will be performed, when pertinent, in cooperation with other experts in the fields of immunology, trace element metabolism, toxicology/pathology and molecular microbiology at our own, as well as at other institutions.

Specific issues to be studied regarding environmental pollutants as disease-promoting agents:

The animals will be infected with gastrointestinal CB3 (i.p.) or respiratory influenza and C.p. (i.n.) infections and the disease progression and uptake and distribution of metal pollutants studied. Exposure will be performed both as in previous studies through the food and drinking water, but also in chambers using aerosol exposure.

In these disease models lymphocyte subpopulation (T-, B-, NK-cells, makrophages, etc.) dynamics will be studied in the blood (FACS analysis) as well as in organs with inflammatory lesions (immuno-histochemistry) (3-5,14,15). Virus in infected organs (brain, lungs, heart, pancreas) will be determined by an *in situ* hybridization technique (6,17,25) or by a quantitative count of viruses in these organs (coxsackie and influenza infections), as well as estimation of the mutation frequency (so far CB3 infection) performed by nucleotide sequence analysis (PCR) of the viral genome. The same quantitative RT-PCR technique that we use for C.p. detection in human tissues (28) will be used in these experimental studies. ELISA-technique is used to monitor cytokine levels and RT-PCR to quantitatively study induction of various metal binding proteins (such as metallothionein variants in lungs, brain, liver and kidneys, and expression of metal transporting proteins) during ongoing disease. The trace metal concentrations will be studied both in blood and infected tissues (ICP-MS). The tissue uptake and distribution of the metals in health and disease will be studied with nuclear microscopy or determined by impulse counting (in selected organs) or by autoradiography (micro or whole body) of labelled compounds (Lindh et al 1996; refs. see CV).

Presentation of results and time table

Results will be published in international scientific journals with an editorial board.

During the first year of the funding period focus will be on comparing effects of gastrointestinal and inhalation exposure of potentially toxic metals (Ni, Cd, Hg) in the well-established coxsackievirus (CB3) infection. The influenza and C.p. infections will also be established for subsequent disease-promoting studies.

During the second year of the funding period the influenza and C.p. infections will be used in exposure studies of the above mentioned metals and results compared with the coxsackievirus infection. In addition, depending on obtained results, other pollutants of environmental significance will be studied

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Educational merits

Bachelor of Science, Uppsala University, Uppsala October 1, 1976.
Courses in points (p); Social Human environment (toxicology, physiology, etc.) (20p), Chemistry (40p), Technical biology (Biochemistry, physiology, technical equipment, etc.) (40p), Zoophysiology/Microbiology (20p), Zoophysiology (20p), Immunology (lectures) (10p).

Ph.D. in Zoophysiology, Uppsala University, June 1, 1983.
Graduate studies at Uppsala University, Uppsala in points (p); Experimental animal research (5p), Techniques in cell physiology (5p), Methods of biochemical analysis and enzymological techniques (5p), Basic literature course (Lehninger: Biochemistry; Ganong: Medical physiology; Dyson: Cell Biology) (16p), Statistics for biologists and earth scientists (5p), Biological nuclide techniques and radio ecology (5p), Methodology in clinical studies of metabolism and nutrition. Graduate studies at Rutgers University, New Brunswick, USA in credits (cr); Bio-aspects of stress (3cr), Advanced studies (seminars) (1cr).

Ass. Prof. Experimental infectious medicine, Faculty of Medicine, Uppsala, Feb 23, 1990.
Courses within the Faculty of Medicine; Educational course for teachers within the Faculty of Medicine, and Work and environmental medical toxicology.

Professor (adjunct), Experimental infectious medicine, Faculty of Medicine, Uppsala University, Uppsala, Jan 1, 2003.

Research merits

U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Frederick, Md., USA.
Laboratories of Disease and Environmental Stress, Bureau of Biological Research, Rutgers University, NJ., USA.

Scientific merits

Supervisor for eight Degree Projects in Toxicology/Pharmacology/Medicine.
Member of Examining Committee (3 times) regarding public defence of the Doctoral Thesis.
Advisor to 2 Doctorate Candidates, Department of Infectious Diseases, Uppsala University. Thesis defence 1999 and 2002.
Outside expert in the appointment of a Full Professor, Medical College of Virginia, Virginia Commonwealth University, Virginia.
Member of the Editorial Board for the international journal Biological Trace Element Research, Humana Press Inc, NJ, USA (ISSN 0163-4984). Member since January 1, 2003.

Professional work experiences

Toxicologist at the Astra Corporation, Södertälje, Sweden.
Division Chief at the Biological Division, National Laboratory of Forensic Science,Linköping, Sweden.
Study Director at Toxicology and Safety Assessment, Pharmacia & Upjohn, Helsingborg.
Toxicologist at the Toxicological Division, National Food Administration, Uppsala, Sweden.

Other merits in toxicology

Ad hoc expert of the Scientific Committee for Food's (SCF) working group on Food Additives (regularly since February 1997), European Commission, Directorate XXIV, Brussels.
Ad hoc expert of the Committee for Veterinary Medicinal Products (CVMP). The European Agency for the Evaluation of Medicinal Products (EMEA), London.
Ad hoc expert of the Committee for Proprietary Medicinal Products (CPMP). The European Agency for the Evaluation of Medicinal Products (EMEA), London.

SELECTED ORIGINAL PUBLICATIONS

1) Ilbäck N-G., G Friman, WR Beisel, AJ Johnsson. Sequential metabolic alterations in the myocardium during influenza and tularemia in the mouse. Infect. Immun. 45:491-497, 1984.
2) Ilbäck N-G., G Friman, WR Beisel, AJ Johnsson, RF Berendt. Modifying effects of exercise on clinical course and biochemical response in influenza and tularemia in mice. Infect. Immun. 45:498-504, 1984.
3) Ilbäck N-G., J Fohlman, G Friman. The protective effect of selenium on the development of coxsackievirus B3 induced inflammatory lesions in the murine myocardium. J. Trace Elem. Exp. Med. 2:257-266, 1989.

4) Ilbäck N-G., A Mohammed, J Fohlman, G Friman. Cardiovascular lipid accumulation with coxsackie B virus infection in mice. Am. J. Pathol. 136:159-167, 1990.
5) Fohlman J., G Friman, N-G Ilbäck, Å Åkesson, S Huber. A qualitative and quantitative method for in situ characterization of the inflammatory response in experimental myocarditis. Acta Pathol. Microbiol. Immunol. Scand. (APMIS) 98:559-567, 1990.
6) Fohlman J., L Wesslén, N-G Ilbäck, G Friman. Segregation of the inflammatory reaction and viral appearance in myocarditis. EOS-Journal of Immunology and Immunopharmacology 10:153-155, 1990.
7) Ilbäck N-G. Effects of methyl mercury exposure on spleen and blood natural killer (NK) cell activity in the mouse. Toxicology 67:117-124, 1991.
8) Ilbäck N-G., J Sundberg, A Oskarsson. Methyl mercury exposure via placenta and milk impair natural killer (NK) cell function in rats. Toxicol. Lett. 58:149-158, 1991.
9) Ilbäck N-G., J Fohlman, G Friman, A Wicklund-Glynn. Altered distribution of ^{109}Cadmium in mice during viral infection. Toxicology 71:193-202, 1992.
10) Funseth E., N-G Ilbäck. Effects of 2.3.7.8-tetrachlorodibenzo-p-dioxin on blood and spleen natural killer (NK) cell activity in the mouse. Toxicol. Lett. 60:247-256, 1992.
11) Ilbäck N-G., J Fohlman, G Friman. A common viral infection can change nickel target organ distribution. Toxicol. Appl. Pharmacol. 113:166-170, 1992.
12) Wiklund-Glynn A., N-G Ilbäck, D Brabencova, L Carlsson, E-C Enqvist, E Netzel, A Oskarsson. Influence of sodium-selenite on ^{203}Hg absorption, distribution and elimination in male mice exposed to methyl-^{203}Hg. Biol. Trace Elem. Res. 39:91-107, 1993.
13) Funseth E., N-G Ilbäck. Coxsackievirus B3 infection alters the uptake of 2.3.7.8-tetrachloro-dibenzo-p-dioxin in the mouse. Toxicology 90:29-38, 1994.
14) Ilbäck N-G., J Fohlman, G Friman. Changed distribution and immune effects of nickel augment viral-induced inflammatory heart lesions in mice. Toxicology 91:203-219, 1994
15) Ilbäck N-G., J Fohlman, G Friman, A Ehrnst. Immune responses and resistance to viral-induced myocarditis in mice exposed to cadmium. Chemosphere 29:1145-1154, 1994.
16) Ilbäck N-G., U Lindh, J Fohlman, G Friman. New aspects from murine Coxsackie B3 myocarditis - focus on heavy metals. Eur. Heart J. 16:20-24, 1995.
17) Ilbäck N-G., L Wesslén, J Fohlman, G Friman. Effects of methyl mercury on cytokines, inflammation and virus clearance in a common viral infection (Coxsackie B3 myocarditis). Toxicol. Lett. 89:19-28, 1996.
18) Ilbäck N-G., J Fohlman, G Friman. Effects of selenium supplementation on virus-induced inflammatory heart disease. Biol. Trace Elem. Res. 63:51-66, 1998.
19) Wicklund-Glynn A., Y Lindh, E Funseth, N-G Ilbäck. The intestinal absorption of cadmium increases during a common viral infection (Coxsackievirus B3) in mice. Chem. Biol. Interact. 113:79-89, 1998.
20) Funseth E., U Lindh, L Wesslén, G Friman, N-G Ilbäck. Trace element changes in the myocardium during Coxsackievirus B3 myocarditis in the mouse. Biol. Trace Element Res. 76:149-160, 2000.
21) Funseth E., A Wicklund-Glynn, G Friman, N-G Ilbäck. Redistribution of accumulated 2.3.7.8-tetrachloro-dibenzo-p-dioxin during Coxsackievirus B3 infection in the mouse. Toxicol. Lett. 116:131-141, 2000.
22) Ilbäck N-G., U Lindh, L Wesslén, J Fohlman, G Friman. Trace element distribution in heart tissue sections studied by nuclear microscopy is changed in Coxsackie B3 myocarditis in methyl mercury exposed mice. Biol. Trace Element Res. 78:131-147, 2000.
23) Funseth E., U Lindh, G Friman, N-G Ilbäck. Relation between trace element levels in plasma and myocardium during Coxsackievirus B3 myocarditis in the mouse. BioMetals 13:361-367, 2000.
24) Funseth E., M Påhlman, M-J Eloranta, G Friman, N-G Ilbäck. Effects of coxsackievirus B3 infection on the acute-phase protein metallothionein and on cytochrome P450 involved in the detoxification processes of TCDD in the mouse. Sci. Total Environ. 284:37-47, 2002.
25) Funseth E., L Wesslén, U Lindh, G Friman, N-G Ilbäck. Effects of 2.3.7.8-tetrachlorodibenzo-p-dioxin on trace elements, inflammation and viral clearance in the myocardium during Coxsackievirus B3 infection in mice. Sci. Total Environ. 284:135-147, 2002.
26) Ilbäck N-G., G Benyamin, U Lindh, G Friman. Sequential changes in Fe, Cu and Zn in target organs during early Coxsackie virus B3 infection in mice. Biol. Trace Elem. Res. 91:111-124, 2003.
27) Ilbäck N-G., G Benyamin, U Lindh, G Friman. Trace element changes in the pancreas during early Coxsacievirus B3 infection in mice. Pancreas 26:190-196, 2003.
28) Nyström-Rosander C., U Lindh, N-G Ilbäck, E Hjelm, O Lindqvist, S Thelin, G Friman. Interactions between *Chlamydia pneumoniae* and trace elements – a possible link to aortic valve sclerosis. Biol. Trace Elem. Res. 91:97-110, 2003.
29) Nyström-Rosander C., U Lindh, G Friman, O Lindqvist, S Thelin, N-G Ilbäck. Trace element changes in sclerotic heart valves from patients are expressed in their blood. BioMetals 00:00-00, 2003 (in press).
30) Ilbäck N-G., A Glynn, L Wikberg, E Netzel, U Lindh. Metallothionein is induced and trace element balance changed in target organs of a common viral infection. Toxicology 00:00-00, 2003 (submitted).