

Pubblicazioni Scientifiche

Articoli su Riviste

Libri e Capitoli di Libri

Comunicazioni Congressuali

LEGENDA

N° Pubblicazione	Tipo di Pubblicazione
<i>Istituto di</i>	TITOLO DELLA PUBBLICAZIONE
<i>Autori</i>	Riassunto
<i>In</i>	

1

Rivista recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Coccini T.,
Randine G.,
Castoldi A.F.,
Acerbi D.,
Manzo L.

In: *Environmental
Research*; 2007; 103;
2: 229-237.

METHYLMERCURY INTERACTION WITH LYMPHOCYTE CHOLINERGIC MUSCARINIC RECEPTORS IN DEVELOPING RATS.

Cerebral cholinergic muscarinic receptors (MR) have been suggested as one of the sensitive biochemical endpoints of the central nervous system altered by developmental exposure to the widespread seafood contaminant methylmercury (MeHg). In adult rats, MeHg has been shown to alter MR binding both in the brain and lymphocytes, supporting the use of MR in blood cells as a surrogate marker of CNS changes. The effects of MeHg have been evaluated on rat lymphocyte MR binding (using [3H]QNB as specific muscarinic ligand) in vivo (after perinatal exposure) and in vitro. For comparison, in vitro studies were also performed on human lymphocytes. Exposure to 1 mg MeHg/kg/day during pregnancy and lactation (from GD7 to PND7) significantly enhanced lymphocyte MR density in both adult and young rats 21 days after delivery, with a more pronounced effect in the mothers (B(max) increase of 139%) than in the male offspring (+49%) and female offspring (+73%) as compared with their respective controls (33±4, 41±8, and 37±4 fmol/million cells), in accordance with the higher Hg levels detected in the adult blood (11.3±2.2 microg/mL) than in pups (1.3±0.4 microg/L in both genders). A lower MeHg dose (0.5 mg/kg/day) was without any effect on lymphocyte MRs. In in vitro studies, MeHg was an almost equipotent inhibitor of (3)H-QNB binding to rat and human lymphocyte MRs (IC50 values were 4.1±0.29, 5.2±0.51, and 5.0±0.9 microM for total rat lymphocytes, rat T lymphocytes, and total human lymphocytes, respectively). Notably, the IC50 values for MeHg to lymphocyte MRs were comparable to the Hg levels reached in blood (5-50 microM) of the PND21 rats exposed to MeHg. The finding that the MR binding is a target for the effects of MeHg in peripheral blood cells is in accordance with our previous data in brain [Coccini et al., 2006. Effects of developmental co-exposure to methylmercury and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153) on cholinergic muscarinic receptors in rat brain. *Neurotoxicology*, in press], and supports the use of this peripheral endpoint as a biomarker of MeHg-induced cerebral muscarinic alterations. The similarity of MeHg IC50 binding data between human and rat in peripheral tissues suggests the possible application of such biomarker to humans exposed to environmental chemicals.

2

Rivista recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Coccini T.,
Roda E.,
Castoldi A.F.,
Goldoni M.,
Poli D.,
Bernocchi G.,
Manzo L.

In: *Toxicology*; 2007; 238;
1: 34-48.

PERINATAL CO-EXPOSURE TO METHYLMERCURY AND PCB153 OR PCB126 IN RATS ALTERS THE CEREBRAL CHOLINERGIC MUSCARINIC RECEPTORS AT WEANING AND PUBERTY.

In the last few decades, combined exposure to methylmercury (MeHg) and polychlorinated biphenyls (PCBs) from fish and seafood, and their potentially interactive effects on neurodevelopment, have been giving increasing cause for concern. We examined the combined effects of MeHg and either a non-dioxin PCB (PCB153) or a dioxin-like PCB (PCB126) congener on the developing brain cholinergic muscarinic receptors (MRs). These receptors are known to play a major role in many central functions including higher cognitive processes and the modulation of extrapyramidal motor activity. MRs in pup rat brains diminished following prenatal and lactational exposure, from gestational day [GD]7 to postnatal day [PND]21, to MeHg (0.5 mg/kgbodyweight[bw]/day), PCB153 (5 mg/kgbw/day), and PCB126 (100 ng/kg/day), alone or in combination. Total MR density, as well as M1, M2, and M3 receptor subtypes of the weanling and pubertal rats, were affected in a brain-area-, gender-, time- and compound-dependent fashion. MeHg decreased (by 15-20%) the total MR density in a delayed (PND36) manner in the cerebral cortex of both genders, and early (at weaning) in the cerebellum of both genders, with the effect lasting until puberty (in males only). MeHg decreased the ACh M1- and M3-immunopositive neurons in the cerebral cortex and also increased the M2-immunopositive Bergmann glia in the cerebellum. PCB153 also induced a delayed (PND36) decrease (of 20%) in total MR number in the cerebellum of the male offspring and in the cerebral cortex of both genders. The latter effect was coupled with a decrease in ACh M1- and ACh M3-immunopositive neuron populations. PCB126 decreased (by 30-40%) total MR density in a gender-dependent manner, males being more sensitive than females. The effect was evident early (at PND21) and lasted until puberty in the cerebellum, while it was observed later (at PND36) in the cerebral cortex. The M1 and M3 receptors were similarly affected by PCB126. Co-exposure to MeHg and either PCB153 or PCB126 had the same effect on the cerebral MRs as exposure to each compound alone. The results rule out additive or synergistic interactions between MeHg and PCB153 or PCB126 on MRs in the brain areas examined. Some early-onset changes persisted until puberty, while other modifications became manifest only at the advanced time point (PND36), when the brain levels of total Hg, PCB153, and PCB126 had declined. These data support the ability of MeHg and PCBs to induce delayed neurotoxicity after developmental exposure.

3

Rivista recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Corsini E,
Codecà I,
Mangiaratti S.,
Birindelli S.,
Minoia C.,
Turci R.,
Viviani B.,
Facchi A.,
Vitelli N.,
Lucchi L.,
Galli C.L.,
Marinovich M.,
Colosio C.

In: *Toxicology and
Applied Pharmacology*;
2007; 222; 2: 202-210.

IMMUNOMODULATORY EFFECTS OF THE HERBICIDE PROPANIL ON CYTOKINE PRODUCTION IN HUMANS: IN VIVO AND IN VITRO EXPOSURE.

Propanil, 3,4-dichloropropionanilide, a commonly used herbicide, has been shown to induce effects on the mouse immune system. The aim of this study was to assess the immunotoxicity of propanil in occupationally exposed agricultural workers and to characterize its molecular mechanism of action. Seven agricultural workers intermittently exposed to propanil and 7 healthy matched controls entered the study. Data were collected through physical examination, and laboratory investigations addressed at the main serum, cellular, and functional immune parameters. The levels of exposure were assessed by determining the urine concentration of the major propanil metabolite, 3,4-dichloroaniline. The investigation of serum, cellular, and functional immune parameters suggested that propanil exposure results in a modest immunomodulatory effect, characterized by an increase in the plasma level of IgG(1) and in LPS-induced IL-6 release and, by a reduction in PHA-induced IL-10 and IFN release, associated with a reduced IFN/IL-4 ratio. As observed, following in vivo exposure, in vitro treatment of human peripheral blood leukocytes with propanil resulted in a dose-dependent reduction in PHA-induced IFN-gamma and IL-10 production, while LPS-induced TNF-alpha production was not affected indicating a direct effect of propanil on selected immune parameters. We demonstrated that propanil interfering with PHA-induced intracellular calcium increase modulated IL-10 and IFN-gamma transcription and translation, which indicates that propanil acts on early events triggered by PHA. Overall, our results suggest that human exposure to propanil has slight immunomodulatory effects, and point out that the inhibition of the PHA-induced intracellular calcium rise is an important target of propanil. These findings improve our understanding of the mechanism underlying propanil-induced immunotoxicity.

4

Rivista recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Fonte R.,
Agosti A.,
Scafa F.,
Candura S.M.

In: *Haematologica*; 2007;
92; 3.

ANAEMIA AND ABDOMINAL PAIN DUE TO OCCUPATIONAL LEAD POISONING.

We describe a 47-year-old patient with chronic anaemia with basophilic stippling of erythrocytes, recurrent abdominal colics, discoloration of gums, sensitive polyneuropathy to the four limbs, hyperuricaemia, hepatosteatosi with raised transaminases, and a long ignored history of lead exposure in a battery recycling plant. The diagnosis of poisoning was confirmed by high lead levels in the blood and urine, decreased erythrocyte delta-aminolevulinic acid dehydratase (ALA-D), raised erythrocyte zinc protoporphyrin (ZP), and elevated urinary excretion of porphyrins. Chelation with EDTA resulted in increased urinary lead excretion, gradual improvement of the clinical picture, and progressive normalization of lead biomarkers. The case highlights the importance of occupational anamnesis for the diagnosis of lead poisoning, an uncommon condition which may mimic a variety of internal and surgical diseases. Since antiquity, lead has been extensively mined, produced, and utilized in a variety of industrial settings, such as metallurgy, construction, production of plastics, ceramics, paints and pigments. Lead and its compounds are systemic toxicants, and a wide range of adverse health effects (including haematological, gastrointestinal, neuropsychiatric, cardiovascular, renal, endocrine, and reproductive disorders) has been observed in exposed workers. The general population (particularly children) may also be exposed to toxic lead levels due to air, soil, food and water contamination. Thanks to the improvement of workplace hygienic conditions, the pathological picture of occupational lead poisoning (plumbism, saturnism) has gradually become less serious, at least in the most industrialized countries, and has progressively changed into aspecific, subclinical manifestations. We describe here an unusual case (nowadays) of anaemia and recurrent abdominal pain due to lead poisoning from battery recycling.

5**Rivista recensita su Index Medicus e/o Science Citation Index**

Istituto di
PAVIA

Johansson C.,
Castoldi A.F.,
Onishchenko N.,
Manzo L.,
Vahter M.,
Ceccatelli S.

In: *Neurotoxicity
Research*; 2007; 11;
3-4: 241-260.

NEUROBEHAVIOURAL AND MOLECULAR CHANGES INDUCED BY METHYLMERCURY EXPOSURE DURING DEVELOPMENT.

There is an increasing body of evidence on the possible environmental influence on neurodevelopmental and neurodegenerative disorders. Both experimental and epidemiological studies have demonstrated the distinctive susceptibility of the developing brain to environmental factors such as lead, mercury and polychlorinated biphenyls at levels of exposure that have no detectable effects in adults. Methylmercury (MeHg) has long been known to affect neurodevelopment in both humans and experimental animals. Neurobehavioural effects reported include altered motoric function and memory and learning disabilities. In addition, there is evidence from recent experimental neurodevelopmental studies that MeHg can induce depression-like behaviour. Several mechanisms have been suggested from in vivo- and in vitro-studies, such as effects on neurotransmitter systems, induction of oxidative stress and disruption of microtubules and intracellular calcium homeostasis. Recent in vitro data show that very low levels of MeHg can inhibit neuronal differentiation of neural stem cells. This review summarises what is currently known about the neurodevelopmental effects of MeHg and consider the strength of different experimental approaches to study the effects of environmentally relevant exposure in vivo and in vitro.

6**Rivista recensita su Index Medicus e/o Science Citation Index**

Istituto di
PAVIA

Minoia C.,
Ronchi A.,
Gaggeri R.,
Guzzi G.,
Severi G.

In: *Science of the Total
Environment*; 2007; 381;
1-3: 331.

CORRELATING BLOOD MERCURY AND DENTAL AMALGAMS.

In their report showing the relationship between sources of mercury and its levels in human whole blood, Gundacker et al. (2006) write that dental amalgams are a significant source of mercury but did not provide details, in the methods section, about how they calculated the number of dental amalgam fillings among participants. In order to minimize the effect of uncertainty regarding the size and extension of a dental amalgam filling area - we suggest to have the number of mercury amalgam surfaces, both as occlusal and total surfaces - determined by a trained dentist ([Kingman et al., 1998], [Mark Richardson and Allan, 1996], [Apostoli et al., 2002] and [Minoia et al., 2006]).

When the clinical details about the number of amalgam areas are unaccounted for, as the authors include solely the gross number of dental amalgam restorations instead of total and/or occlusal surfaces, there may be a weak or negative relation between the blood mercury concentrations and the number of amalgams ([Apostoli et al., 2002] and [Minoia et al., 2006]).

Moreover, given the high levels of intraoral mercury vapor released during mastication of chewing-gum ([Lorscheider et al., 1995] and [Clarkson, 2002]) - reaching the bloodstream primarily via the lungs and consequently causing accumulation of mercury vapor in red blood cells - it would have been valuable to consider the use of chewing-gum as potential confounding variable associated with exposure to dental amalgam.

7**Rivista recensita su Index Medicus e/o Science Citation Index**

Istituto di
PAVIA

Minoia C.,
Ronchi A.,
Veronese I.,
Giussani A.,
Guzzi G.

In: *Occupational and
Environmental Medicine*;
2007; 64; 856.

THE CONFOUNDING EFFECTS OF INTRA-ORAL METALS IN SALIVARY BIOMARKERS.

In their education article in the March issue (*Occup Environ Med* 2007; 64: 202-10), Koh and Koh interestingly propose that measurements of heavy metals (for example, lead and cadmium) in saliva may be a novel and promising approach to occupational health, revealing the patient's risk of systemic exposure to toxicant. We would like to share our experience regarding the assessment of metals in saliva matrices.

8**Rivista recensita su Index Medicus e/o Science Citation Index***Istituto di
PAVIA**Moscato G.,
Yacoub M.R.**In: Monaldi Archives
for Chest Disease;
2007; 67; 3: 154-158.***WORLD TRADE CENTER DISASTER: SHORT AND MEDIUM TERM HEALTH OUTCOME.**

Several studies related to September 11 World Trade Center (WTC) terrorist attack have been conducted in order to monitor physical and mental health in the population at risk in the short and medium term. In this paper the main health consequences in the exposed subjects 6 years after the disaster, including ocular, gastrointestinal, respiratory and psychological effects are described and discussed.

9**Rivista recensita su Index Medicus e/o Science Citation Index***Istituto di
PAVIA**Pino A.,
Alimonti A.,
Botrè F.,
Minoia C.,
Bocca B.,
Conti M.E.**In: Rapid Communications
in Mass Spectrometry;
2007; 21; 12: 1900-1906.***DETERMINATION OF TWENTY-FIVE ELEMENTS IN LICHENS BY SECTOR FIELD INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY AND MICROWAVE-ASSISTED ACID DIGESTION.**

A simple and efficient digestion method for rapid sample preparation and quantification of 25 chemical elements in lichens by sector field inductively coupled plasma mass spectrometry is described. A microwave (MW)-assisted acid digestion was carried out at atmospheric pressure simultaneously handling up to 80 samples in screw-capped disposable polystyrene tubes. This digestion procedure was compared with the established MW digestion in closed vessels in order to examine its potential applicability in routine analysis for environmental monitoring. Three certified reference materials, i.e. BCR 482 (lichens), BCR 62 (olive leaves) and BCR 100 (beech leaves), as well as a small set of real samples were analyzed. Limits of quantification, accuracy and precision of the method were assessed. The majority of the elements were totally recovered from the lichens and from the other vegetable matrices. Low contamination risk, simplicity, time-saving, and applicability in routine analyses make this method very suitable for use in extensive screening campaigns.

10**Rivista recensita su Index Medicus e/o Science Citation Index***Istituto di
PAVIA**Rosso G.L.,
Feola M.,
Morena L.,
Menardi E.,
Racca E.,
Vado A.,
Rossetti G.,
Peano E.,
Candura S.M.**In: Giornale Italiano
di Medicina del Lavoro
ed Ergonomia; 2007;
29; 2: 166-169.***NEURALLY-MEDIATED SYNCOPE AND OCCUPATIONAL ACCIDENTS: PREVENTION STRATEGIES AND CASE REPORT.**

A bus driver came to our observation after an occupational traffic accident due to a syncopal event. The positive result of the tilt testing demonstrated the neurally-mediated nature of the syncope. The accident involved approximately 40 people (all the bus passengers), fortunately without severe injuries or deaths. The described episode indicates the need for a procedural algorithm, commonly approved, applicable in the field of prevention, for those occupational categories with severe accident risk. Indeed, the possibility exists to identify at least a part of the subjects predisposed to neurally-mediated syncope. Fundamental steps for such screening are history taking (looking for previous events, familiarity), the physical examination (useful, for example, to exclude orthostatic hypotension or carotid sinus syncope), and, in particular, the tilt testing, a diagnostic investigation recommended for all the workers who have had a previous syncope and are at high occupational accident risk. Moreover, the reported case recalls the need to strengthen the collaboration between the cardiologist and the occupational health physician.

11

Rivista recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Sacchi M.,
Daglio M.,
Feletti T.,
Lanave M.,
Candura S.M.,
Strosselli M.

In: *La Medicina del Lavoro*;
2007; 98; 1: 64-72.

ACCIDENTS WITH RISK OF BLOOD-BORNE INFECTIONS IN OBSTETRICIANS: ANALYSIS OF A HOSPITAL CASE RECORDS.

Background: Health care workers (HCW) are at high risk of accidental contact with biological fluids. In spite of extensive recommendations concerning HCW accidents continue to be frequent and seem to be related to specific factors.

Objectives: To evaluate the factors influencing risk of blood-borne infections in a particular category of HCW-obstetricians, and obtain information useful for prevention guidelines.

Methods: Data were obtained from the exposure registers of nursing and of the Emergency Ward staff where HCW first report after accidental contact with biological fluids.

Results: Accidents with risk of blood-borne diseases were more frequent in obstetricians with lower job seniority. They usually occurred between 8 a.m. and 4 p.m., in the patient's room. The hands and face (particularly the eyes) were the body parts more often involved. In almost half of the accidents, the worker was not wearing any personal protective device. Although some contacts were with infected blood, no seroconversion occurred.

Conclusions: Obstetricians are at high risk of contact with biological fluids. Prevention requires a global strategy including the availability of protective and safety devices, as well as worker education, especially concerning the use of such devices, the application of the universal rules of prevention and the improvement of risk awareness. An adequate post-exposure management of accidents is also required.

12

Rivista recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Settimi L.,
Davanzo F.,
Carbone P.,
Sesana F.,
Locatelli C.,
Farina M.L.,
Maiozzi P.,
Roazzi P.,
Maccari F.,
Macchi L.,
Fanuzzi A.

In: *Annali Istituto
Superiore di Sanità*;
2007; 43; 3: 287-294.

SURVEILLANCE OF TOXIC EXPOSURES: THE PILOT EXPERIENCE OF THE POISON CONTROL CENTERS OF MILAN, PAVIA AND BERGAMO IN 2006.

Between 1 February and 31 March 2006, the Poison Control Centers (PPC) active in Lombardy collaborated with an integrated surveillance system carried out in Piedmont during the Olympic Games 2006. The collaborating PPC notified to the system 697 human cases of exposure occurred in Piedmont during the observation period. Among these cases, 70% were exposed accidentally, 40% were 6 years old or younger, and 45% reported at least a clinical effect. The agents more frequently reported were: cleaning substances (household) (110 cases), fumes/gases/vapors (63 cases, comprising 38 cases accidentally exposed to carbon monoxide), and sedative/hypnotics/antipsychotics (53 cases). Although very limited, the available observations focused the attention on specific hazards and were able to highlight the potential of a toxic exposure surveillance system based on the information reported by the Italian PPC.

13

Rivista recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Sottani C.,
Turci R.,
Schierl R.,
Gaggeri R.,
Barbieri A.,
Violante F.S.,
Minoia C.

In: *Rapid
Communications in Mass
Spectrometry*; 2007; 21;
7: 1289-1296.

SIMULTANEOUS DETERMINATION OF GEMCITABINE, TAXOL, CYCLOPHOSPHAMIDE AND IFOSFAMIDE IN WIPE SAMPLES BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY/TANDEM MASS SPECTROMETRY: PROTOCOL OF VALIDATION AND UNCERTAINTY OF MEASUREMENT.

Measurable levels of anticancer agents are still detected on work surfaces in health-care settings. However, application of recent guidelines for the protection of workers' safety and health has resulted in lowered contamination levels. To assess occupational exposure to antineoplastic agents, very sensitive and specific procedures for environmental sampling and analysis are therefore needed. In the present study an assay for simultaneous determination of gemcitabine, taxol, cyclophosphamide, and ifosfamide in wipe samples, using two internal standards (trofosfamide and cephalomannine), was developed and validated by high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS). Solid-phase extraction (SPE) was used for



▶ 13

Rivista recensita su Index Medicus e/o Science Citation Index

sample concentration and cleanup. The assay was found to be linear up to 1000 ng/wipe, with limits of quantitation of 25.0 ng/wipe for gemcitabine and taxol, and 12.5 ng/wipe for cyclophosphamide and ifosfamide. In order to investigate the effectiveness of the surface sampling, removal efficiency tests were repeated on different types of surfaces. Recovery rates of between 62 and 81% were obtained at two contamination levels (50.0 and 250 ng/100 cm²). Precision and trueness were determined on three different days. The within-day precision was found to be always less than 12.1% for all the analytes. The overall precision, expressed as relative standard deviation (RSD), was always less than 9.4%. Recoveries varying from 75.0 (gemcitabine) to 95.0% (taxol) were obtained at three levels. In order to obtain a quantitative indication of the quality of the result, the overall uncertainty of measurement (UOM) was evaluated according to the EURACHEM/CITAC guide. The relative combined uncertainty was found to be always less than 9.5%. The relative expanded uncertainty was also calculated, at three contamination levels.

14

Rivista recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Vittadini G.,
Bandirali M.

In: *La Medicina
del Lavoro*; 2007; 98;
6: 521-526.

ALCOHOL AND WORK: REMAINING SOBER AND RETURN TO WORK.

One of the most complex alcohol-driven problems is the job loss and the subsequent attempts to return to a profession activity.

In order to better understand the issue, and epidemiologic investigation was carried out on a group of 162 alcoholics whilst hospitalised in a specialised clinic. The outcome shows the importance of remaining sober to keep or to be returned to one's own job. Unfortunately, local resources at hand, first of all joining an auto-mutual- help group, re still too little known and this clearly underemployed.

Therefore, an informative action within companies is highly desirable. Those alcoholics suffering from serious illness, especially mental ones represent a different issues.

For these people a higher involvement of public authorities is desirable in creating protected job openings.

15

Poster

Centro di
PADOVA

Slama R.,
Thiebaugeorges O.,
Goua V.,
Sacco P.,
Annesi-Maesano I.,
Charles M.,
et al.

In: *19th Conference
of International Society
for Environmental
Epidemiology (ISEE);
Mexico City,
5-9 Sept. 2007.*

MATERNAL PERSONAL EXPOSURE TO BENZENE DURING PREGNANCY AND INTRA-UTERINE GROWTH.

Several studies reported associations between maternal air pollution levels during pregnancy and birth weight corrected for gestational duration.

In the former studies, exposure to air pollutants was usually assessed from the measurements performed at the closest air quality monitoring station (sometimes located several km away). More seldom, distance-weighted traffic intensity metrics or land-use regression models have been used.

Very few studies relied on personal dosimetry of air pollutants; these were focused on fine particulate matter (PM_{2.5} or polycyclic aromatic hydrocarbons (Choi et al., 2006). To our knowledge, the potential effects of benzene, a component of traffic-related air pollution, on intra-uterine growth, have very little been studied. Our aim was to characterize the effect of maternal exposure to benzene during pregnancy on the intra-uterine growth of her offspring.

When the cohort's women came for a clinical examination taking place between 24 and 28 gestational weeks, they were proposed to carry a Radiello passive air sampler during 7 consecutive days.

In this cohort of 287 women, we observed a decreased birth weight and head circumference at birth in relation to maternal exposure to benzene above 4 mg/m³ during the second trimester of pregnancy. The estimated effect of benzene exposure was not monotonous. The association between benzene exposure and head circumference assessed in utero was weaker than that with head circumference at birth but exhibited a similar pattern.

However, further studies are needed to confirm that in our population road traffic was the main source of variability in exposure levels to benzene. Since traffic-related benzene levels are correlated with other traffic-related pollutants, the associations observed here with benzene might in part or totally be due to other traffic-related air pollutants.

16

Comunicazione scientifica recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Coccini T.,
Castoldi A.F.,
Roda E.,
Marafante E.,
Cimino-Reale G.,
Casati B.,
Manzo L.

In: *Toxicology Letters*;
2007; 172; S179-S180.

GENDER-, TIME- AND BRAIN AREA-DEPENDENT MODULATION OF MUSCARINIC RECEPTOR DENSITY AND GENE EXPRESSION IN RATS PERINATALLY EXPOSED TO METHYLMERCURY AND PCB153.

Methylmercury (MeHg) and polychlorinated biphenyls (PCBs) are ubiquitous environmental contaminants that alter cognitive function in both humans and animals. Using saturation 3H-QNB binding studies and mRNA-microarrays techniques, the density (Bmax) of total cholinergic muscarinic receptors (MRs) and gene expression pathways of MR subtypes (M1-M3 vs M2-M4) were investigated in the cerebellum and cerebral cortex of rats at weaning (PND21) and puberty (PND36) after maternal exposure (GD7-PND21) to MeHg (0.5 mg/kg/day) and PCB153 (5 mg/kg/day) alone or in combination.

In cerebellum, MeHg decreased the MR density of 15% in both male and female rats at PND21 (control Bmax values (mean \pm SE): 71 \pm 14 and 76 \pm 14 fmol/mg protein, respectively). Males, but not females, displayed a MR Bmax reduction at PND36 after perinatal exposure to MeHg and/or PCB153.

In cerebral cortex, the MRs were affected in a delayed manner (PND36) in both genders by all treatments. The decrease in receptor number induced by either compound given alone was similar in magnitude (about 15%) to that caused by the co-exposure. Control values were 796.0 \pm 121.8 and 793.9 \pm 91.9 fmol/mg protein for male and female pups, respectively.

Data on gene expression showed relevant differences between male/female at both PND21 and PND36. Concerning MRs, the co-exposure to MeHg and PCB153 induced the modulation of genes in the M1-M3 and M2-M4 signalling pathways, particularly in the cerebellum of females.

These results demonstrate persistent gender- and age-related differences in MR density and their associated gene expression pathways following the co-exposure to MeHg and PCB153.

Supp. by European Commission (FOOD-CT-2003-506543) and Italian Ministry of Health.

17

Comunicazione scientifica recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Coccini T.,
Bongiorno A.,
Castoldi A.F.,
Roda E.,
Vitalone A.,
Costa L.G.,
Goldoni M.,
Poli D.,
Manzo L.

In: *Toxicology Letters*;
2007; 172; 192.

EFFECTS OF GESTATIONAL AND LACTATIONAL EXPOSURE TO PCB126 AND METHYLMERCURY ON CIRCULATING STEROID HORMONE LEVELS AT WEANING AND PUBERTY IN THE RAT.

PCBs have been reported to possess estrogenic or anti-estrogenic properties depending on the congener type and the experimental system used. In vivo methylmercury (MeHg), which often occurs in food together with PCBs, can also disrupt endocrine function.

This study assessed whether maternal consumption of the dioxin-like PCB126 congener (100 ng/kg b.w./day), alone or combined with MeHg (0.5 mg/kg b.w./day), throughout gestation and lactation (GD7-PND21) affected the serum concentrations of 17 beta-estradiol (E2) and testosterone (T) in male and female rat offspring at weaning (PND21) and puberty (PND36). Sex hormones were measured by radioimmunoassay kits.

Concerning E2 levels, PCB126 and/or MeHg were devoid of any effect in weanling rats of either gender (controls: 8.68 \pm 2.90 pg/ml in males; 9.94 \pm 2.63 pg/ml in females). At puberty, males (but not females) treated with PCB126 alone showed a 60% reduction in the hormone circulating levels. Such decrease persisted in the co-presence of MeHg.

Concerning T levels, a 25% decrease (as compared to controls) was detected in PND21 males exposed to PCB126 alone, which was still evident at puberty. By contrast, in PND21 females only the combined PCB126-MeHg exposure resulted in a significant (66%) reduction of T concentrations (control: 1.09 \pm 1.06 ng/ml). Developmental exposure to PCB126 alone or combined with MeHg alters circulating steroid hormone levels in a different manner according to gender, age and hormone considered. MeHg, by itself, does not seem to act as an endocrine disruptor, at least on these end-points, during development. (Supported by the European Commission, FOOD-CT-2003-506543 and the Italian Ministry of Health).

18**Comunicazione scientifica recensita su Index Medicus e/o Science Citation Index***Istituto di
PAVIA**Coccini T.,
Roda E.,
Castoldi A.F.,
Crevani A.,
Manzo L.**In: Toxicology Letters;
2007; 172; 180.***DEVELOPMENTAL CO-EXPOSURE TO METHYLMERCURY AND PCB153 OR PCB126 AFFECTS CEREBRAL CHOLINERGIC MUSCARINIC RECEPTORS AT WEANING AND PUBERTY IN RATS.**

Combined effects of methylmercury (MeHg) and either the dioxin-like PCB126 or the non-dioxin-like PCB153 have been examined on the developing brain muscarinic receptors (MRs).

Following exposure (GD7-PND21) to MeHg (0.5 mg/kg/day), PCB153 (5 mg/kg/day), and PCB126 (100 ng/kg/day), alone or combined, MR density (by 3H-QNB saturation binding), and M1-, M2-, M3-receptor subtypes (by immunohistochemistry) of weanling and pubertal rats, were affected in a brain-area-, gender-, time- and compound-dependent fashion. MeHg decreased (15-20%), in both genders, the MR density in a delayed (PND36) manner in the cerebral cortex, and early (at weaning) in the cerebellum, with the latter effect lasting until puberty (in males only). MeHg decreased M1- and M3-immunopositive neurons in cerebral cortex and increased M2-immunopositive Bergmann glia in cerebellum. PCB153 induced a delayed MRs decrease (20%) in cerebellum of males and in cerebral cortex of both genders. PCB126 also decreased (by 30-40%) MRs but in males only: the effect was evident early and lasted until puberty in cerebellum, while it appeared at PND36 in the cortex. M1- and M3-receptors were similarly affected by both PCBs.

Co-exposure to MeHg and either PCB-congener had the same effect on MRs as exposure to each compound alone. The results rule out additive/synergistic interactions between these compounds on cerebral MRs.

Some early-onset changes persisted until puberty, other modifications became manifest only at PND36, when the brain levels of Hg, PCB153, and PCB126 had declined. These data support the ability of MeHg and PCBs to induce delayed neurotoxicity after developmental exposure.

Supp. by EU (FOOD-CT-2003-506543) and Italian Ministry of Health.

19**Comunicazione scientifica recensita su Index Medicus e/o Science Citation Index***Istituto di
PAVIA**Manzo L.,
Castoldi A.F.,
Coccini T.,
Lonla E.,
Marafante E.,
Sarigiannis D.A.**In: Journées de
Neurologie de Langue
Française; 2007; 163;
246.***CONTAMINANTS ALIMENTAIRES ET PATHOLOGIES NEUROTOXIQUES.**

Plusieurs contaminants alimentaires (ex: méthylmercure, plomb, arsénique, polychlorobiphényles, toxine botulinique, toxines marines, contaminants des boissons alcooliques comme le méthanol) sont neurotoxiques pour les humains. Les effets toxiques et le mécanisme d'action des ces substances sont assez connus grâce aux recherches sur animaux de laboratoire ou sur modèles cellulaires mais les neurologues les connaissent peu car les cas cliniques sont très rares.

Plusieurs incertitudes existent sur la classification clinique des symptômes de l'exposition à des contaminants alimentaires neurotoxiques. Parfois, l'exposition prolongée à de faibles doses contenues dans les aliments détermine des effets subtils difficiles à diagnostiquer comme par exemple des petites altérations psychologiques et comportementales.

Certains contaminants alimentaires sont plus nocifs pour les personnes en pleine croissance que pour des sujets adultes. Selon une hypothèse, mercure, plomb et aluminium peuvent être liés aux maladies neurodégénératives chez l'homme. Un récent thème de recherche s'occupe du développement d'indicateurs biochimiques aptes à révéler la présence précoce d'altérations même avant l'apparition des symptômes cliniques. Par exemple, un test sur la densité des récepteurs muscariniques lymphocytaires a été appliqué sur des patients alcooliques tout comme chez une cohorte d'enfants exposés au méthylmercure dans les îles Faroe. D'autres biomarqueurs de neurotoxicité pourront dériver d'une meilleure connaissance des mécanismes moléculaires surtout à travers le progrès de la biologie moléculaire et la toxicogénomique.

20

Comunicazione scientifica recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Moscato G.,
Perfetti L.,
Pignatti P.,
Cappelli I.

In: *European Respiratory
Journal*; 2007; 30; 156.

OCCUPATIONAL RHINITIS TO SODIUM ALENDRONATE.

We describe a case of occupational rhinitis (OR) to sodium alendronate (SA) in a worker of a pharmaceutical company.

Case Report: a 39 yr old atopic woman had been employed for 10 years in the packaging section of a pharmaceutical manufacture factory. Two months before being referred to our centre she started to present nasal itching, rhinorrhoea and cough, when exposed to powdered SA. The symptoms occurred at work or after the work shift, improved on weekends and holidays. No symptoms were reported by the other employees. When the subject was admitted to our centre she had not been exposed to SA for 6 months. Spirometry was normal: metacholine and bronchodilator test were negative. Prick and patch tests with SA in saline (1/100) were positive. The same tests were negative in 10 non-exposed controls (5 atopic). Specific Inhalation Challenge (SIC) was performed with the occupational method (pouring the substance from one dish to another in an inhalation chamber). On a control day the patient was exposed to lactose. There was no significant change in nasal symptom score and PNIF (Peak Nasal Inspiratory Flow). The following day she was exposed to SA 10 mg dissolved in lactose for 60. Exposure reproduced rhinitis symptoms and yielded a significant fall of PNIF. SIC with SA was repeated in the same patient after levocetirizine (5 mg), and also in a healthy control (34 yr old atopic, non-exposed woman), with no symptoms and no fall of PNIF. *Conclusion:* To our knowledge, this is the first case of OR due to SA. Diagnosis of occupational disease was confirmed by specific inhalation challenges (SIC). The positive prick tests and the negative response to SIC after levocetirizine suggest that mast cells may be involved in the mechanisms.

21

Comunicazione scientifica recensita su Index Medicus e/o Science Citation Index

Istituto di
PAVIA

Roda E.,
Castoldi A.F.,
Coccini T.,
Mustarelli P.,
Quartarone E.,
Profumo A.,
Merli D.,
Fagnoni M.,
Manzo L.

In: *Toxicology Letters*;
2007; 172; 235-236.

IN VITRO TOXICITY ASSESSMENT OF SINGLE- AND MULTI-WALLED CARBON NANOTUBES IN HUMAN ASTROCYTOMA AND LUNG CARCINOMA CELLS.

The need to assess the safety of carbon nanotubes has arisen from their wide application in commercial, environmental and medical sectors. This study was undertaken to characterize the physicochemical properties of single-walled carbon nanotubes (SWCN), multi-walled carbon nanotubes (MWCN), and functionalized MW (MW-COOH and MW-NH₂), and to assess their cytotoxicity in human astrocytoma D384-cells and lung carcinoma A549-cells, using the MTT assay and calcein/propidium iodide (PI) staining. Both the as-received and the modified nanotubes were characterized by means of thermal analysis (TGA), infrared spectroscopy, and atomic force microscopy chiefly to check the degree of functionalization. The cells were exposed to the nanomaterials (0.1-100 ug/ml) for 24, 48 and 72h in medium containing 10% FCS. In D384 cells MTT results revealed a strong cytotoxicity (50%) of SW after 24h-exposure already at 0.1 ug/ml, without further changes at higher concentrations or longer incubation times. At all time-points MTT metabolism was decreased by 50% by all the other compounds at 10 ug/ml and with no exacerbation at the higher dose. Similar results were obtained with A549 cells. Experiments using calcein/PI staining did not confirm MTT cytotoxicity data neither in D384- nor in A549-cells. The viability of these cells was not affected by any nanotube at any concentration or time of exposure, with the exception of the positive control SiO₂. The present results suggest the need of a careful examination of carbon nanotubes toxic effects by means of multiple tests to circumvent the possible problem of artifactual results due to the interference of nanomaterials with the dye markers employed.

22

Comunicazione scientifica recensita su Index Medicus e/o Science Citation Index

Istituto di
VERUNO

Aliciato P.,
Russo F.,
De Lisa R.,
Alliata E.,
Galante M.

In: *Giornale Italiano
di Medicina del Lavoro
ed Ergonomia*; 2007;
29; 1: 131-132.

TECNICHE ALTERNATIVE ALLA TRADIZIONALE MOVIMENTAZIONE MANUALE DEL PAZIENTE: LA CINESTETICA.

Le affezioni cronico-degenerative della colonna vertebrale sono al 2° posto nella lista dei 10 problemi di salute più rilevanti nei luoghi di lavoro secondo il NIOSH (National Institute of Occupational Safety and Health); in base i dati disponibili, il settore sanitario è tra i più colpiti e si riscontra un progressivo aumento delle segnalazioni da parte di operatori sanitari addetti alla movimentazione del paziente.

La cronicità che frequentemente caratterizza tali affezioni, con esacerbazioni, graduale ingravescenza del quadro clinico, rappresenta un aggiuntivo fattore limitante con conseguenze sulla capacità lavorativa del soggetto: progressiva incapacità di svolgere le attività ordinarie della propria mansione, impossibilità a fronteggiare incrementi del carico lavorativo, estrema difficoltà di ricollocamento del soggetto.

Dati recenti relativi agli USA, riferiti alla popolazione generale, hanno evidenziato che:

- la lombalgia è la causa principale di limitazione lavorativa in soggetti con meno di 45 aa (assenza media per malattia: 28,6 giorni ogni 100 lavoratori);
- gli indennizzi per patologie professionali della colonna lombare assorbono il 33% dei costi totali (il 16% del totale delle richieste di risarcimento è sotto la voce "low back pain");
- la lombalgia è la prima causa di richiesta di visita medica straordinaria;
- è la quinta causa di ricovero ospedaliero;
- è la terza più frequente causa di intervento chirurgico.

In Italia, manca una raccolta di dati precisa e dettagliata come quella americana citata. Secondo dati ISTAT, le affezioni acute dell'apparato locomotore sono al 2° posto nella prevalenza di patologie acute, e al 2° posto tra le cause di invalidità civile. Gli infortuni denunciati hanno incidenza e prevalenza costanti.

Per il settore sanitario, un'indagine svolta da Marena et al nel 1997 presso l'IRCCS Policlinico S. Matteo ha evidenziato che, su 1573 operatori sanitari (ripartiti in infermieri professionali, generici, caposala, ausiliari, operatori tecnici dei servizi sanitari ed economici), l'86.4% degli operatori ha anamnesi positiva per disturbi lombosacrali; di questi nell'80.4% tale sintomatologia era insorta negli ultimi 3 mesi.

Dopo diversi anni di utilizzo di varie tipologie di ausili meccanici, è nato un crescente interesse verso tecnologie alternative alla tradizionale movimentazione manuale dei pazienti, al fine di eseguire manovre che tutelino sia il paziente sia l'operatore sanitario.

Infatti, se da un lato il personale infermieristico numericamente insufficiente e l'elevata incidenza degli infortuni sul lavoro orientano verso misure di tutela per l'operatore, ad esempio utilizzo di ausili meccanici, dall'altro l'eccessivo ricorso a questi ultimi potrebbe inficiare l'autonomia e le capacità funzionali residue del paziente.

Queste diverse esigenze sono presenti ancora di più nel contesto della riabilitazione dove il nursing, oltre alle valenze abituali, diventa parte integrante del progetto riabilitativo sviluppato e condotto dall'équipe multidisciplinare. La movimentazione può diventare così non un atto fine a se stesso, in cui il paziente ha un ruolo passivo, ma un ulteriore momento riabilitativo dove il paziente, guidato dall'infermiere, può apprendere le strategie più adatte per il pieno utilizzo delle proprie abilità ottenendo così il maggior recupero delle proprie funzioni motorie e cognitive con minor disagio psico-fisico.

In questo contesto, una delle possibili tecniche alternative di approccio al paziente è rappresentata dalla cinestetica, nata, in fase teorica, alla University of California ad opera di Hatch nel 1972 e, come fase pratica, applicativa a largo raggio nel 1974, grazie all'apporto professionale della dott.ssa Maietta. Il termine risulta dalla combinazione di due parole di origine greca "kinesis" = movimento e "aesthetics" = percezione, e si distingue dall'approccio tradizionale per la componente "percettiva" del movimento dell'operatore rispetto all'ambiente e al paziente e, soprattutto, per l'autopercezione del paziente del proprio movimento e delle proprie sensazioni.

23**Rivista non recensita**

Centro di
PADOVA

Skov H.,
Sørensen B.T.,
Landis M.S.,
Johnson M.S.,
Sacco P.,
Goodsite M.E.,
Lohse C.,
Christiansen K.S.

In: *Environmental
Chemistry*; 2007; 4;
2: 75-80.

PERFORMANCE OF A NEW DIFFUSIVE SAMPLER FOR Hg⁰ DETERMINATION IN THE TROPOSPHERE.

Mercury behaves uniquely in the atmosphere due to its volatility and long lifetime. The existing methods for measuring atmospheric mercury are either expensive or labour intensive. The present paper presents a new measurement technique, the diffusive sampler, that is portable, inexpensive, easy to use, and does not need a power supply. The sampler is sufficiently sensitive that it can measure mercury at low ambient levels with an exposure time of 1 to 3 days. The sampler is based on the Radiello diffusive sampler, which was used to collect volatile organic compounds. In the present paper, the method is validated under controlled laboratory conditions. The uptake rate of the Radiello diffusive sampler is determined using known concentrations of gaseous elemental mercury, and is measured as a function of wind speed, relative humidity and temperature. The Radiello sampler has a detection limit of 0.14 ngm⁻³ for 1 day of exposure and thus can be used to measure mercury concentrations at the low levels found in ambient air. The Radiello sampler is therefore useful for mapping concentrations close to sources and sinks, in addition to ambient concentrations. For example, the sampler can be used to describe the geographical extent of Arctic mercury depletion episodes where gaseous elemental mercury is removed and stays close to 0 ngm⁻³ for days, and it can be a powerful tool for mapping gradients around point sources and other areas of interest.

24**Rivista non recensita**

Istituto di
PAVIA

Turci R.,
Minoia C.

In: *Hospital Pharmacy
Europe*; 2007; 34: 42-43.

SAFE HANDLING OF CYTOSTATIC DRUGS AND QUALITY ASSURANCE IN EXPOSURE ASSESSMENT.

Occupational exposure to cytostatic drugs has long been recognised as a health hazard, and the Laboratory for Environmental and Toxicological Testing in Pavia, Italy, has been working on quality assurance in this field for more than a decade.

25**Capitolo di Libro in italiano**

Istituto di
PAVIA

Castoldi A.F.,
Manzo L.

In: *Klaassen CD (ed).
Casarett & Doull's
Tossicologia (6ª edizione
italiana, coordinata da
W. Balduini et al.). EMSI;
Roma, 2007; 115-141.*

ASSORBIMENTO, DISTRIBUZIONE ED ESCREZIONE DELLE SOSTANZE TOSSICHE.

Il capitolo esamina i processi di assorbimento, distribuzione ed escrezione delle sostanze tossiche.

26**Capitolo di Libro in italiano**

Istituto di
PAVIA

Coccini T.,
Manzo L.

In: Klaassen CD (ed).
Casarett & Doull's
Tossicologia (6ª edizione
italiana, coordinata
da W. Balduini et al.).
EMS, Roma, 2007;
143-236.

BIOTRASFORMAZIONE DEGLI XENOBIOTICI.

Il capitolo descrive i processi di biotrasformazione degli xenobiotici.

27**Capitolo di Libro in italiano**

Istituto di
PAVIA

Marrubini G.,
Manzo L.

In: Klaassen CD (ed).
Casarett & Doull's
Tossicologia (6ª edizione
italiana, coordinata
da W. Balduini et al.).
EMS, Roma, 2007;
237-250.

TOSSICOCINETICA.

Il capitolo illustra i principi di tossicocinetica.

28**Capitolo di Libro in italiano**

Istituto di
PAVIA

Prevaldi C.,
Petrolini V.

In: Tartaglino B. (ed).
Farmaci e Procedure
in Medicina d'Urgenza,
II edizione. C.G. Edizioni
Medico Scientifiche;
Torino, 2007; 964-980.

DECONTAMINAZIONE DEL PAZIENTE.

L'assorbimento dei veleni può avvenire attraverso varie vie (gastroenterica, cutanea, inalatoria, parenterale, ecc.). In alcuni casi è possibile utilizzare tecniche atte a rimuovere il veleno prima che venga assorbito e somministrare prontamente antidoti che consentono di diminuire drasticamente il carico tossico intervenendo sull'assorbimento. Nel caso di sostanze caustiche, la decontaminazione ha anche lo scopo di limitare i danni locali.

29**Comunicazione scientifica pubblicata su atti congressuali***Centro di
PADOVA**Cocheo C.,
Frigerio F.,
Andreani G.**In: 25° Congresso
Nazionale AIDII; Ancona,
20-22 Giugno 2007.***APPLICAZIONE DEL D.L. 187/05 NELLA CANTIERISTICA NAVALE.**

Negli stabilimenti Fincantieri viene eseguito l'intero ciclo della costruzione navale: dal taglio della lamiera, all'allestimento finale. L'esposizione a vibrazioni del sistema mano-braccio, per il personale Fincantieri, è stata ridotta nel tempo ed è attualmente legata a lavorazioni specifiche che si verificano per qualche settimana in un anno. Nel presente lavoro è illustrato l'approccio adottato per la valutazione di esposizione del personale alle vibrazioni come richiesto dal D.Lgs. 187/05 in un contesto dove la quantificazione dei tempi di esposizione su base giornaliera o settimanale può risultare particolarmente complessa.

Per gli utensili manuali è stata riscontrata una variabilità nei risultati molto superiore a quella dovuta ai mezzi di trasporto a causa delle differenze fra le diverse lavorazioni e, qualche volta, della difficoltà a simulare in officina particolari lavorazioni che si svolgono normalmente a bordo nave.

Le gru e i carrozzone non risultano costituire un rischio significativo per l'esposizione alle vibrazioni in quanto presentano valori di A_{wmax} ampiamente inferiori a $0,5 m \cdot s^{-2}$.

Sono stati individuati numerosi utensili con $A_{wsum} > 5 m \cdot s^{-2}$.

Per le figure professionali che impiegano frequentemente questi utensili, in particolare motoseghe e avvitatori a impulso, il rispetto del valore limite per $A(8)$ può essere conseguito solo limitando il tempo di esposizione e tenendo conto della rotazione fra più addetti.

La maggioranza dei lavoratori è classificabile nella classe di rischio $A(8) < 0,5 m \cdot s^{-2}$ per l'esposizione alle vibrazioni trasmesse al corpo intero.

Il superamento del valore di azione, ma non del valore limite, è stato riscontrato solo per il personale che utilizza frequentemente il carrello elevatore sui piazzali del cantiere attraversati dai binari delle gru o connessi per altri motivi.

30**Comunicazione scientifica pubblicata su atti congressuali***Centro di
PADOVA**Cottica D.**In: Atti Corso
di Aggiornamento
- Associazione Italiana
degli Igienisti Industriali;
Chianciano Terme,
8-9 Marzo 2007.***LA VALUTAZIONE DELL'ESPOSIZIONE CUTANEA NELLA DEFINIZIONE DEL RISCHIO CHIMICO E CANCEROGENO.**

A seguito del DLgs. 25/02 è diventata ancor più contingente la valutazione dell'esposizione per via cutanea in termini di contributo all'esposizione professionale ad agenti chimici e cancerogeni. La difficoltà d'elaborare questa valutazione deriva dalla mancanza di linee guida condivise e di metodiche standardizzate. Nel lavoro vengono presentate le Norme disponibili e proposte le possibili soluzioni nonché il contributo che può fornire l'igienista industriale per questa valutazione.

31**Comunicazione scientifica pubblicata su atti congressuali***Centro di
PADOVA**Cottica D.**In: Atti Corso
di Aggiornamento -
Associazione per lo
studio ed il controllo
della contaminazione
ambientale; Politecnico
di Milano; Milano,
7 Maggio 2007.***IL CONTROLLO DELLA CONTAMINAZIONE CHIMICA IN LABORATORIO.**

La valutazione dell'esposizione professionale ad agenti chimici nei Laboratori si esplica prevalentemente attraverso un percorso di analisi documentale che non necessariamente porta ad eseguire monitoraggi ambientali e biologici per la misura degli agenti chimici utilizzati ed i relativi indicatori biologici d'esposizione.

La premessa è indispensabile in considerazione dell'entità, in questo comparto produttivo, delle variabili che devono essere analizzate in un processo di valutazione dell'esposizione ad agenti chimici secondo quanto previsto dal D.Lgs. 626/94 e, in particolare, dal D.Lgs. 25/02 ed ancor prima dal D.Lgs. 66/00 per gli agenti chimici cancerogeni. Le variabili possono essere così riassunte: agenti chimici utilizzati; loro classificazione tossicologica; quantità utilizzate nell'anno e per singola attività/fase operativa; frequenza delle operazioni; contesto operativo; sistemi di prevenzione impiantistica presenti; loro efficienza ed efficacia; procedure operative; professionalità, formazione ed informazione degli operatori; conformità dei DPI e loro utilizzo.

32**Comunicazione scientifica pubblicata su atti congressuali***Centro di
PADOVA**Cottica D.**In: Atti: American
Industrial Hygiene
Conference; Philadelphia,
USA, 02-07 June 2007.***IMPROVING DIFFUSIVE SAMPLING RATE THROUGH A RADIAL DESIGN.
ROUND TABLE "ISSUE AND CONCERNS IN DIFFUSIVE SAMPLING FACTORS
INFLUENCING PERFORMANCE".**

In the diffusive sampler, the adsorbing and the diffusive surfaces are two opposing plane of a closed box. Driven by the concentration gradient, the gaseous molecules pass through the diffusive surface and are trapped from the adsorbing surface. To improve the analytical sensitivity the collected mass should be increased by enlarging the sampling rate Q. Cannot we improve Q then? The answer is to improve the sampler geometry to a radial design. From this idea the Radiello sampler has been developed: the diffusive and adsorbing surfaces are cylindrical and coaxial; a large diffusive surface faces, at a fixed distance, the small surface of a little concentric cartridge. By virtue of radial symmetry, uptake rate is high, since it does not vary linearly but exponentially with the ratio diffusive surface vs diffusive path length.

33**Comunicazione scientifica pubblicata su atti congressuali***Centro di
PADOVA**Cottica D.,
Grignani E.**In: Atti 25° Congresso
Nazionale Associazione
Italiana degli Igienisti
Industriali; Ancona,
20-22 Giugno 2007.***LA VALUTAZIONE DEL RISCHIO ASSOCIATO ALL'ESPOSIZIONE LAVORATIVA
A PARTICELLE NANOMETRICHE: VALUTAZIONE PRELIMINARE ALLE MISURE
STRUMENTALI.**

La nanotecnologia in termini generali riguarda tecnologie che utilizzano o manipolano strutture o materiali che hanno una scala dimensionale da 1 a 100 nm. Accanto alle nanotecnologie, quindi ad una produzione o un utilizzo deliberato di dette strutture chimiche, esiste tutto un vasto campo di situazioni produttive o di ricaduta sugli ambienti di vita in cui la presenza di nanoparticelle può esser prevista. Nell'uno e nell'altro caso la presenza di nanoparticelle può costituire una fonte di rischio chimico e come tale va valutata. Attualmente sono disponibili scarsissime informazioni sulla via d'esposizione dominante, i livelli potenziali d'esposizione e la loro tossicità. In questo lavoro ci si è occupati di quella che viene normalmente definita la valutazione preliminare dell'esposizione ad agenti chimici intesa come lo studio dei processi chimico-fisici e tecnologici alla base della formazione delle nanoparticelle e l'individuazione delle potenziali fonti/situazioni d'esposizione professionale. Scopo del lavoro è quello di fornire indicazioni sui comparti produttivi da esplorare ai fini dell'individuazione di potenziali esposizioni a nanoparticelle, lasciando alle altre relazioni previste nella sessione dedicata alle nanotecnologie lo sviluppo dei temi relativi ai sistemi di campionamento, l'impiego delle nanoparticelle nelle tecnologie civili ed industriali, i meccanismi di tossicità, l'impatto sulla salute.

34**Comunicazione scientifica pubblicata su atti congressuali***Centro di
PADOVA**Sacco P.,
Grignani E.,
Pagani D.,
Quaglio F.,
Zaratin L.**In: Atti del Congresso
Internazionale AIHce
2007 - American
Industrial Hygiene
Conference and
Exhibition; Philadelphia
Pennsylvania (USA),
2-7 Giugno 2007.***MEASUREMENT OF 1,3-BUTADIENE AND ISOPRENE IN WORKPLACE AIR
BY DIFFUSIVE SAMPLING AND THERMAL DESORPTION GC ANALYSIS.**

1,3-butadiene is classified by IARC as probably carcinogenic for humans (group 2A); isoprene is classified as possibly carcinogenic for humans (group 2B). Both compounds are widely used in the production of elastomers. A number of methods allow the measurement of 1,3-butadiene in workplace air, by pumping air through activated charcoal or molecular sieves, followed by solvent or thermal desorption and gas chromatography. More recently, methods based on diffusive sampling onto molecular sieves or graphitised carbon blacks, were proposed. However, the sampling rates of such methods, based on axial diffusion tubes, are lower than 1 ml/min and do not allow ppb level sensitivities. In the present work, a method for measuring 1,3-butadiene and isoprene is presented, based on radial diffusive sampling, thermal desorption and gas chromatography. Two sets of standard atmosphere experiments were carried out to assess the performance of radial diffusive samplers, filled with a graphitised carbon black, for sampling 1,3-butadiene or isoprene, separately. A dynamic exposure chamber, with one to three gaseous dilution steps, was used. The testing conditions were set at 20 °C and 50% RH, exposure time up to 8-hour and concentration levels from the TLV (2 ppm) down to a few ppb. The diffusive sampling rates for 8-hour exposure were in the range 30-40 ml/min. Minimum quantifiable concentrations are as low as 1 ppb, or better. High diffusive sampling rates, combined with enhanced sensitivity offered by thermal desorption, give the method the capability of measuring low concentrations of compounds suspected of carcinogenic properties. The use of diffusive sampling allows the industrial hygienists to overcome explosive hazards, when sampling in chemical plants or other restricted working environments.

35

Comunicazione scientifica pubblicata su atti congressuali

Centro di
PADOVA

Sacco P.,
Carrieri M.,
Boaretto C.,
Grignani E.,
Salamoi F.,
Bartolucci G.B.,
Cottica D.

In: *Atti del 13° Convegno di Igiene Industriale "Le giornate di Corvara"; Corvara (BZ), 26-28 Marzo 2007.*

CONFRONTO FRA METODI DI CAMPIONAMENTO AD ASPIRAZIONE FORZATA E TECNICHE DIFFUSIVE A SIMMETRIA RADIALE: APPLICAZIONI IN AMBIENTE DI LAVORO E DI VITA.

Nella pratica dell'igiene industriale e dell'igiene ambientale si sono affermati, negli ultimi anni, i campionatori a diffusione, in quanto presentano numerosi vantaggi rispetto ai sistemi di campionamento ad aspirazione forzata: non richiedono energia elettrica: sono quindi leggeri, poco ingombranti, economici e possono essere impiegati anche in aree a rischio d'incendio ed esplosione. I campionatori diffusivi a simmetria radiale, caratterizzati da una favorevole costante geometrica, presentano portate di campionamento paragonabili a quelle utilizzate con i sistemi ad aspirazione forzata.

Dal momento che l'utilizzo di questi sistemi di campionamento è relativamente recente nella pratica igienistica, sono ancora pochi i metodi di campionamento e analisi della qualità dell'aria, basati sul campionamento diffusivo. Fra questi si possono citare il metodo europeo standardizzato per la misura del benzene in aria ambiente e i metodi pubblicati in Gran Bretagna per gli ambienti di lavoro.

Nelle applicazioni non contemplate dai suddetti metodi di campionamento diffusivo, è quindi sentita l'esigenza di confrontare direttamente i risultati di misura con quelli ottenuti con i metodi convenzionali, ad aspirazione forzata. In questo lavoro vengono presentati i risultati del confronto fra metodi diffusivi e metodi ad aspirazione forzata per diversi agenti chimici in diverse applicazioni: percloroetilene in ambiente di lavoro; benzene in ambiente di lavoro; benzene e toluene in ambiente di lavoro a bassi livelli di esposizione; benzene, toluene, etilbenzene e xileni in ambiente di vita.

36

Comunicazione scientifica pubblicata su atti congressuali

Centro di
PADOVA

Sacco P.,
Pagani D.,
Quaglio F.,
Zaratin L.,
Cottica D.,
Grignani E.

In: *25° Congresso Nazionale AIDII; Ancona, 20-22 Giugno 2007.*

STUDIO PRELIMINARE PER IL CAMPIONAMENTO DIFFUSIVO DI COMPOSTI ORGANICI CANCEROGENI AERODISPERSI IN AMBIENTI DI LAVORO.

Il cloruro di vinile, l'1,3-butadiene e l'isoprene sono monomeri largamente usati nell'industria chimica per la produzione di elastomeri, materie plastiche ad altri prodotti chimici.

Scopo di questo lavoro è lo studio di fattibilità di un metodo per il campionamento di cloruro di vinile, 1,3-butadiene e isoprene in aria, adatto ad essere utilizzato in ambienti di lavoro con rischio di esplosione. Sono stati utilizzati campionatori diffusivi a simmetria radiale, riempiti con un adsorbente adatto al deadsorbimento termico (Carbopack X). Per ciascuna delle tre sostanze sono stati condotti tre test di esposizione, della durata di 8 ore, in atmosfere standard di concentrazione 15 ppb, 150 ppb e 2 ppm rispettivamente, a 20 °C di temperatura e 50% di umidità relativa.

L'analisi dei campioni diffusivi esposti alle atmosfere standard è stata eseguita per deadsorbimento termico seguito da gascromatografia capillare accoppiata alla spettrometria di massa.

Per l'1,3-butadiene è stata determinata una portata di campionamento per diffusione pari a $29,1 \pm 1,3$ ml/min; per l'isoprene è stata determinato un valore medio di $42,2 \pm 4,5$ ml/min, con una leggera tendenza ad aumentare con l'aumento della concentrazione. Per il cloruro di vinile sono stati determinati valori di portata variabili da 2,3 a 3,2 ml/min, molto più bassi di quelli prevedibili sulla base della diffusività della sostanza e della costante geometrica del campionatore.

I risultati degli esperimenti preliminari eseguiti confermano quindi la possibilità di mettere a punto un metodo di campionamento per l'1,3-butadiene e l'isoprene aerodispersi in ambiente di lavoro, basato sul campionamento diffusivo a simmetria radiale, con un materiale adsorbente adatto al deadsorbimento termico. Per il cloruro di vinile sono necessarie ulteriori ricerche per migliorare il rendimento di captazione e deadsorbimento.

37**Comunicazione scientifica pubblicata su atti congressuali**Centro di
PADOVAZaratin L.,
Sacco P.,
Cocheo C.,
Cottica D.,
Grignani E.*In: International
Conference on Healthy
Air - Better Work 2007;
Helsinki, 29-31 Maggio
2007; 43.***SETUP OF A PROTOCOL FOR THE MEASUREMENT OF VOLATILE ORGANIC COMPOUNDS AND ALDEHYDES IN INDOOR AIR BY MEANS OF DIFFUSIVE SAMPLING.**

In view of the setting up of an Observatory for Indoor Air Quality in France a multidisciplinary approach was chosen, in order to gather a database about health threats faced in indoor environments. In this framework, a measurement protocol was set up for a large number of volatile organic compounds: aliphatic and aromatic hydrocarbons (including benzene), aldehydes (including formaldehyde), esters, terpenes, glycol ethers, halogenated compounds. In indoor air these compounds may be emitted by a number of sources, like building materials, furniture and household products.

The aim of this work was the development of the sampling and analysis protocol for the above mentioned polluting agents in residential or non-industrial indoor environments, based on 7-day diffusive sampling. For aldehydes a radial diffusive sampler filled with DNPH-coated floril was used. For the other volatile compounds two different configurations were tested: axial tube and radial symmetry sampler, with different adsorbing media, compatible with thermal desorption.

The diffusive uptake rates were experimentally determined by exposure to standard atmospheres; the corresponding uncertainty values were determined according to ISO Guide for uncertainty of measurements.

For aldehydes, uptake rate values were determined for nine compounds (including formaldehyde) with extended uncertainty values from 13 to 23% in the concentration range from about 2 to 80 µg/m³. For VOCs the best results were obtained by radial diffusive samplers filled with Carbograph 4, with uptake rate values ranging from 6.4 ml/min for alpha pinene to 27.1 ml/min for styrene and extended uncertainty values from 10% (toluene, xylenes) to 99% (n-dodecane).

38**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIA

Faga A.

*In: Atti 56° Congresso
Nazionale SICPRE; 2007.***CHIRURGIA PLASTICA: UNA PROFESSIONE AL MASCHILE?**

Analisi della attuale posizione della donna nell'ambito delle attività mediche in generale e della chirurgia plastica in particolare, con riferimento al ruolo femminile nella Storia della Medicina e alle vigenti normative sulle Pari Opportunità.

39**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIAButera R.,
Bacis G.,
Faraoni L.,
Petroli V.,
Locatelli C.,
Farina M.L.,
Manzo L.*In: Atti del XXVII
International Congress
of the European
Association of Poisons
Centres and Clinical
Toxicologists (EAPCCT);
Atene (Grecia),
1-4 Maggio 2007;
45; 387.***THERAPEUTIC MISADVENTURES WITH VITAMIN K IN NEWBORNS: CONSEQUENCES OF NEW RECOMMENDATIONS.**

Background: Optimal methods for the prevention of late vitamin K deficiency bleeding in the newborn have been the subject of a considerable debate in recent years and remain to be fully resolved. After concerns about carcinogenicity of intramuscular vitamin K administration, the oral route has been preferred. It has been shown that orally treated breastfed infants have to continue vitamin K supplementation during the first months of life. Since a long time, this has been accomplished with the administration of vitamin K 1 mg once a week, based on the sole available, licensed medicinal product containing vitamin K (Konakion® phytomenadione 20 milligrams/ml, 1 drop = 1 mg). In 2004, according to the result of a Dutch study, the National Society of Neonatology recommended the use of a new therapeutic regimen of 25 micrograms/day. In the meantime, a product containing phytomenadione 20 micrograms/ml (Vita K®) was licensed to the market as nutritional supplement agent.

Objective: To describe the occurrence of therapeutic errors during vitamin K oral supplementation in infants after the license to the market of a new low dosage product.

Methods: A retrospective analysis of two years (2004-2005) Bergamo and Pavia Poison Centers records was performed in order to identify pediatric cases of inadvertent oral administration of high doses vitamin K. The previous 2-year period was analyzed for comparison. Patients demographic and clinical data were reviewed. The causes of error were investigated.



▶ 39

Comunicazione scientifica pubblicata su atti congressuali

Results: In the study period, a total of 30 cases (age: 3 days - 6 months) were identified, compared to 2-4 cases/year observed in the two previous years. Patients received 2 to 3600 mg vitamin K; in 41% of cases repeated large doses were administered. No relevant toxic effects were observed. All cases but 3 were related to the use of Konakion® instead of Vita K®. The causes of error were identified in (i) a dispensing error made by the pharmacist, who misunderstood the proprietary name of the prescribed product (Vita K®) as the name of the active ingredient, and in (ii) a generic request for vitamin K made by parents. In both cases, pharmacists delivered the commonly used, licensed medicinal product Konakion®, which was subsequently administered by parents to the infants at the drops regimen prescribed for Vita K® (20-25 drops/day, corresponding with Konakion® to 20-25 milligrams/day vitamin K).

Conclusion: Our experience suggests that sudden changes in prescription strategies can cause therapeutic errors that involve the liability of health professionals. Their alerting before such changes take place might reduce the risk of error.

40

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Butera R.,
Eleftheriou J.,
Signorini S.,
Versino M.,
Fazzi E.,
Farina M.L.,
Manzo L.

In: *Atti dell'18th Annual ENTIS Meeting; Helsinki (Finlandia), 8-10 Giugno 2007; 46-47.*

CIGUATERA POISONING IN EARLY PREGNANCY AND SEVERE VISUAL IMPAIRMENT IN THE CHILD: A CASE REPORT.

Introduction: Ciguatera is a well known mild to severe poisoning caused by ingestion of toxins produced by certain dinoflagellates (e.g. Gambierdiscus toxicus) and accumulated in the fish flesh through the trophic chain. Ciguatera is characterized mainly by gastrointestinal and neurological symptoms. Few case reports have suggested that ciguatoxins cross the placenta and may affect the fetus.

Case Report: A 33 year-old pregnant woman ate barracuda while on vacation in Cuba. At that time she was unaware of the pregnancy, being at the 3rd gestational week. She developed diarrhea and vomiting within a few hours, followed by weakness, generalized pruritus, distal extremity paresthesias, and dysesthesias with reversed thermal sensation. She was treated with oral fluids, antiemetics and antihistamines. All neurophysiological studies performed 7 days after poisoning were normal except for the latent tetany test, described in detail elsewhere. Within 6 weeks after fish ingestion, all symptoms resolved. The course of the pregnancy was normal and no other illness or drug consumption was reported. Prenatal screenings for congenital and genetic diseases were negative. At 39 weeks she delivered by cesarean section an apparently healthy male infant (3190 g). Visual impairment was suspected at the age of 3-4 months, because of difficulty following moving objects. Clinical examination performed at the age of 6 months showed pendular nystagmus and normal pupils response to light; visual acuity was markedly reduced (0.6 cycles/degree, corresponding to 0.2/10); fundus examination showed mild aspecific pigment deposits; visual evoked potentials (VEP) were normal for age; electroretinography (ERG) was borderline in the left eye. The child was followed until the age of 4.5 years. Diagnostic assessment was repeated: nystagmus disappeared while visual acuity remained low (1/10 at 2 m, 1.5/10 at 40 cm) with moderate photophobia. Brain magnetic resonance imaging was negative, VEP demonstrated bilateral delay; ERG showed photopic abnormalities. No cognitive impairment was present (QI 110).

Discussion: In the patient described here, the clinical course is similar to that of congenital retinal dystrophies, except for the normal pupils response to light and the disappearance of nystagmus at the age of 4 years. However a role of the in utero ciguatoxin exposure can not be completely excluded. Nervous system is the main target organ of ciguatoxin toxicity. Toxicokinetics are poorly investigated, but it has been postulated that ciguatoxins can persist in the body for a long period; consistently, clinical experiences showed that ciguatera can remain subclinical for months after acute poisoning and can be unmasked by physical activity or selected food consumption. The ability of ciguatoxins to cross placental barrier has been clinically suggested too. Since visual impairment became more evident with age, the value of published experiences suggesting the absence of ocular toxicity is limited by the fact that outcome was assessed at delivery with no prolonged follow-up. Moreover, these reports come from endemic areas with poor socioeconomic conditions, where non life-threatening or major but uneventful defects might be underdiagnosed. If future observations will document other cases of visual impairment after in utero exposure to ciguatoxins, the teratogenic potential of this poisoning should be reconsidered.

41

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIAButera R.,
Eleftheriou J.,
Signorini S.,
Versino M.,
Fazzi E.,
Farina M.L.,
Manzo L.In: *Atti dell'International
Symposium on Algal
Toxins; Trieste,
27-29 Maggio 2007;*
30-31.

CIGUATERA POISONING IN EARLY PREGNANCY AND SEVERE VISUAL IMPAIRMENT IN THE CHILD: A CASE REPORT.

Introduction: Ciguatera is a well known mild to severe poisoning caused by ingestion of toxins produced by certain dinoflagellates (e.g. Gambierdiscus toxicus) and accumulated in the fish flesh through the trophic chain. Ciguatera is characterized mainly by gastrointestinal and neurological symptoms. Few case reports have suggested that ciguatoxins cross the placenta and may affect the fetus.

Case Report: A 33 year-old pregnant woman ate barracuda while on vacation in Cuba. At that time she was unaware of the pregnancy, being at the 3rd gestational week. She developed diarrhea and vomiting within a few hours, followed by weakness, generalized pruritus, distal extremity paresthesias, and dysesthesias with reversed thermal sensation. She was treated with oral fluids, antiemetics and antihistamines. All neurophysiological studies performed 7 days after poisoning were normal except for the latent tetany test, described in detail elsewhere. Within 6 weeks after fish ingestion, all symptoms resolved. The course of the pregnancy was normal and no other illness or drug consumption was reported. Prenatal screenings for congenital and genetic diseases were negative. At 39 weeks she delivered by cesarean section an apparently healthy male infant (3190 g). Visual impairment was suspected at the age of 3-4 months, because of difficulty following moving objects. Clinical examination performed at the age of 6 months showed pendular nystagmus and normal pupils response to light; visual acuity was markedly reduced (0.6 cycles/degree, corresponding to 0.2/10); fundus examination showed mild aspecific pigment deposits; visual evoked potentials (VEP) were normal for age; electroretinography (ERG) was borderline in the left eye. The child was followed until the age of 4.5 years. Diagnostic assessment was repeated: nystagmus disappeared while visual acuity remained low (1/10 at 2 m, 1.5/10 at 40 cm) with moderate photophobia. Brain magnetic resonance imaging was negative, VEP demonstrated bilateral delay; ERG showed photopic abnormalities. No cognitive impairment was present (QI 110).

Discussion: In the patient described here, the clinical course is similar to that of congenital retinal dystrophies, except for the normal pupils response to light and the disappearance of nystagmus at the age of 4 years. However a role of the in utero ciguatoxin exposure can not be completely excluded. Nervous system is the main target organ of ciguatoxin toxicity. Toxicokinetics are poorly investigated, but it has been postulated that ciguatoxins can persist in the body for a long period; consistently, clinical experiences showed that ciguatera can remain subclinical for months after acute poisoning and can be unmasked by physical activity or selected food consumption. The ability of ciguatoxins to cross placental barrier has been clinically suggested too. Since visual impairment became more evident with age, the value of published experiences suggesting the absence of ocular toxicity is limited by the fact that outcome was assessed at delivery with no prolonged follow-up. Moreover, these reports come from endemic areas with poor socioeconomic conditions, where non life-threatening or major but uneventful defects might be underdiagnosed. If future observations will document other cases of visual impairment after in utero exposure to ciguatoxins, the teratogenic potential of this poisoning should be reconsidered.

42

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIAButera R.,
Porro R.In: *Atti della 33ª Giornata
di Studio di Ingegneria
Sanitaria-Ambientale
"L'arsenico nelle acque
destinate al consumo
umano. Nuove tecnologie
di rimozione: esperienze
ed applicazioni"; Brescia,
6 Luglio 2007.*

L'ARSENICO NELLE ACQUE: EFFETTI SULLA SALUTE UMANA.

Numerosi studi hanno collegato l'insorgenza di effetti avversi sulla salute umana all'esposizione cronica ad arsenico attraverso le acque destinate al consumo umano, dove esso è presente in forma inorganica sia come arsenico trivalente (As3+) che pentavalente (As5+). Gli effetti possono manifestarsi dopo molti anni di esposizione. Le prime manifestazioni della tossicità dell'arsenico sono visibili a livello cutaneo, dove appaiono aree di iperpigmentazione e cheratosi, e alle estremità dove la compromissione della vascolarizzazione periferica determina la cosiddetta "malattia del piede nero" (blackfoot disease). Gli effetti che destano maggiori preoccupazioni sono legati all'insorgenza di tumori, specie a carico di vescica, polmone, cute e reni. Peraltro, vi sono anche effetti diversi dal cancro, di tipo endocrino, cardiovascolare e neurologico. Per l'identificazione dei livelli accettabili di arsenico nelle acque, i dati tossicologici derivanti da modelli sperimentali nell'animale di laboratorio sono di scarsa utilità perché poco predittivi degli effetti osservabili nell'uomo; le informazioni sulle quali si basa la caratterizzazione del rischio derivano pertanto dall'analisi degli studi epidemiologici, sui quali esiste una vasta letteratura. Dalle evidenze attuali sembra di poter concludere che, sotto il profilo della prevenzione, il valore limite di 10 ppb di arsenico nelle acque destinate al consumo umano sembra essere un ragionevole compromesso tra i costi di intervento e i benefici per la salute, anche se alcuni Autori suggeriscono il più restrittivo limite di 3 ppb.

43

Comunicazione scientifica pubblicata su atti congressuali*Istituto di
PAVIA**Capodaglio E.M.**In: Atti 7° Safe Patient
Handling and Movement
Conference, Orlando
(FL); March 2007.***RISK ASSESSMENT IN PATIENTS' TRANSFERRING AND ASSISTING IN HEALTH-CARE WORKERS; AN ALTERNATIVE METHOD.**

Risk assessment in health-care workers related to patients' transferring and assisting in Italy is usually performed with the Mapo method (1). Quantitative risk assessment methods have been criticized (2, 3, 4) mainly because of poor adherence to real conditions and to the critical operative aspects. Risk for the health-care workers are not only related to the lifting phases performed (peak load), but also to the postural and static ones, which represent 40-50% of the total work shift, and constitute an independent risk factor (cumulative load) (5, 6, 7, 8). An exhaustive ergonomic approach to prevention should therefore consider also postural load (ie assisting and positioning patients in the bed), patients' motor and behavioural characteristics (ie cooperative or combative), dimensional interfaces between transferring/lifting aids and beds/wheelchairs, work organisation (tasks distribution, breaks, information transferring, ...).

44

Comunicazione scientifica pubblicata su atti congressuali*Istituto di
PAVIA**Capodaglio E.M.,
Draicchio F.**In: Atti Convegno
Nazionale Ergonomia
Applicata: Sanità
e Servizi; Arezzo,
Novembre 2007.***RISCHIO DA MOVIMENTAZIONE MANUALE DEI PAZIENTI: ALCUNE CONSIDERAZIONI DALLA RECENTE LETTERATURA.**

Mentre nella popolazione lavorativa in generale si registra dal 1992 una diminuzione negli incidenti in generale, i disturbi muscoloscheletrici nella popolazione infermieristica continuano a crescere con una prevalenza mondiale del 17% e annuale del 40-50%. Gli interventi preventivi tradizionali (addestramento alle tecniche di movimentazione manuale, lezioni di biomeccanica del rachide) si sono dimostrati inefficaci. Nell'ultima decina di anni si è assistito ad una notevole evoluzione delle attrezzature tecnologiche per la ausiliazione delle manovre di movimentazione dei pazienti, tuttavia spesso non ancora sufficientemente diffuse e conosciute. L'OSHA ha emanato nel 2003 le linee guida per la movimentazione dei pazienti in ambito ospedaliero, che includono le seguenti raccomandazioni: la movimentazione manuale dei pazienti deve essere ridotta al minimo ed eliminata quando possibile; il datore di lavoro deve attuare un processo ergonomico effettivo integrato che includa il supporto manageriale, il coinvolgimento dei lavoratori, l'identificazione dei problemi, la soluzione dei problemi, il report degli incidenti, l'opportunità di addestramento, la valutazione degli interventi ergonomici.

In particolare vengono segnalati, tra le soluzioni di tipo ergonomico (ingegneristiche, amministrative, comportamentali), alcuni interventi pratici dimostratisi efficaci secondo il criterio "evidence-based":

- a) dotazione di ausili per la movimentazione dei pazienti;
- b) protocolli ergonomici di valutazione del livello di dipendenza dei pazienti;
- c) politica del "no-lift";
- d) addestramento all'uso degli ausili;
- e) team dedicato alla movimentazione.

Confrontando questi punti con la situazione attuale in Italia emerge che nel nostro Paese: è ancora scarsa la conoscenza delle diverse tecnologie disponibili per la movimentazione dei pazienti; sono stati attuati alcuni investimenti relativi alle attrezzature, anche se spesso le decisioni in merito sono poco partecipate, l'addestramento relativo non è esauriente e manca la verifica dell'efficacia; la gestione della sicurezza è ancora troppo individuale (solitamente affidata alla figura del RSPP) e poco sistematica, manca il più delle volte il gruppo multidisciplinare dedicato alla movimentazione; la formazione degli operatori viene attuata ma in modo generale, senza dedicare attenzione ad una parte più specifica che investa le problematiche del Reparto e l'uso pratico degli ausili; risulta in genere scarso il supporto manageriale sui problemi operativi; per quanto riguarda la parte di gestione sanitaria risulta carente il report degli incidenti e poco definiti i protocolli di valutazione.

45

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIACapodaglio E.M.,
Draicchio F.,
Bazzini G.In: *Atti Convegno
Nazionale Ergonomia
Applicata: Sanità
e Servizi; Arezzo,
Novembre 2007.*LA VALUTAZIONE DEL RISCHIO DA MOVIMENTAZIONE DEI PAZIENTI
IN OSPEDALE; UNA PROPOSTA INTEGRATIVA.

La valutazione del rischio per gli operatori sanitari addetti alla movimentazione ed assistenza dei pazienti in ospedale segue solitamente in Italia la procedura del metodo quantitativo Mapo attraverso il quale spesso non è possibile comprendere tutte le situazioni critiche operative; la movimentazione del paziente in ospedale si configura infatti sempre più come problema complesso, dai molteplici aspetti, la cui prevenzione deve essere comprensiva di diversi fattori di rischio. Sono stati analizzati i documenti di valutazione del rischio relativo alla movimentazione dei pazienti compilati in 12 RSA e in 35 Reparti di degenza. I documenti sono stati analizzati in riferimento a: metodo applicato e correttezza della procedura; indicazione dei dati grezzi e dei fattori moltiplicativi attribuiti; segnalazione delle criticità operative; proposta degli interventi da attuare; comprensività della situazione reale. In generale si è rilevato che: in parecchi documenti appaiono errori o carenze nell'applicazione del metodo Mapo; la procedura Mapo non garantisce la registrazione di eventuali difficoltà operative e sul carico manuale effettivo; gli interventi amministrativi (es. fornitura di ausili minori, di letti regolabili in altezza, interventi formativi) non vengono specificati in modo sufficiente. Discutendo tali risultati ci pare che la valutazione del rischio dovrebbe prevedere un'integrazione tra il metodo Mapo e altri criteri che risultino più comprensivi delle possibili situazioni critiche, prendendo in considerazione aspetti come la postura ed i movimenti eseguiti dall'operatore, la tecnica di movimentazione adottata, l'organizzazione del lavoro (compreso le situazioni di urgenza), l'attenzione alla disposizione degli spazi e delle infrastrutture, la considerazione della condizione clinica del paziente (capacità residua motoria, possibilità di collaborazione).

46

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIAChiodini A.,
Somaruga C.,
Turci R.,
Vitelli N.,
Minoia C.,
Colosio C.In: *Atti del 7th International
Symposium on Biological
Monitoring; 2007; 141.*HUMAN EXPOSURE TO PERSISTENT ORGANIC POLLUTANTS AND HEALTH
RISK: CURRENT KNOWLEDGE AND PERSPECTIVES.

Purpose: Persistent organic pollutants (POPs) are organic compounds of anthropogenic origin that have an intrinsic resistance to natural degradation processes. These compounds include pesticides (DDT, heptachlor, etc.), and other chemical compounds, such as hexachlorobenzene, polychlorinated biphenyls, polychlorinated dibenzodioxins and polychlorinated dibenzofurans. Although their production and use are now banned in many countries, they are still a matter of great concern due to their persistence and ability to concentrate through the food chain. Since humans are at the top of the food chain, they accumulate lipophilic, persistent compounds in their blood, in adipose tissue, and in breast milk. Humans can be exposed to POPs through diet, occupational accidents, and the environment. Both acute and chronic exposure to POPs may be associated to a wide range of adverse health effects, including cancer, endocrine disruption, immunotoxicity, neurobehavioral and developmental disorders, and birth defects. Body burden data, have been obtained from biological monitoring all over the world. Yet, much has still to be done. In order to collect additional information about human health risks, it is necessary to identify early biomarkers of adverse effects in the general population. Effect-biomarker studies on exposed subjects should therefore be performed.

Methods: A systematic bibliographic research has been conducted on the main international toxicological and medical databases. Key words were "organochlorine compounds AND endocrine disruption, cancer, neurological impairment; PCB AND thyroid hormones, immune system".

Results: The most commonly used biomarker of body burden of POPs is one of the most abundant PCB congener, CB-153, whereas p,p'-DDE is considered to be a good indicator of non-recent exposure to DDT. Both biomarkers can be measured in serum samples, and correction for serum fat content is recommended. Moreover, our study has pointed out the possibility of measuring, in a pre-clinical phase, estrogenic effects, impairment of thyroid hormones synthesis and of glucose metabolism.

Conclusion: It is recommended to carry out biological monitoring activities in which, together with biological indicators of dose, the following pre-clinical effect indicators are measured: T3, T4, TSH; 17beta-Estradiol; Testosterone; Luteinizing Hormone, Follicle-Stimulating Hormone; Sexual Hormone Binding Globulin; Prolactine; Serum Glucose and Glycate Haemoglobine. A pilot experience of such an approach is being prepared by our group, and will be carried out in the next future in an Asian developing country.

47

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIAColosio C.,
Basilicata P.,
Chiodini A.,
Fustinoni S.,
Miraglia N.,
Turci R.,
Simonelli A.,
Somaruga C.,
Vitelli N.,
Minoia C.,
Sannolo N.In: *Atti del 7th International
Symposium on Biological
Monitoring*; 2007; 64.

A COMBINED MODELLING AND MONITORING APPROACH TO PESTICIDE EXPOSURE ASSESSMENT.

Purpose: Exposure assessment is a key element in the overall risk assessment process. However, reliable data can hardly be obtained in pesticide exposure assessment, since a number of factors can affect the repeatability of the measures and, therefore their representativity. This is the reason why algorithms and models are being developed. The aim of this study is to assess the variability of biological exposure measures in agricultural workers in an attempt to compare them with the estimates generated by algorithms.

Methods: 34 subjects working in tomato cultivations in 20 farms located in the south of Italy, exposed to several different active ingredients; 48 vineyard workers mainly exposed to ethylenbisdithiocarbamates, and 12 subjects applying chlorpyrifos in Northern Italy, have been monitored. In order to collect comprehensive exposure data and information on pesticide application method, all participants completed a self-administered enrolment questionnaire. Recent exposure was assessed by measuring appropriate biomarkers in tomato workers, urinary ethylenethiorea in vineyard workers, and urinary 3,5,6-trichloro-2-pyridinol in pesticides applicators exposed to chlorpyrifos. The analytical procedures had been validated, including measurement uncertainty at high, medium, and low concentration levels. A repeated-measures design allowed to assess the reliability of the field data.

Results: The collected data were found to vary widely over time. This finding suggests that biological monitoring could provide information on recent exposure only, which may be a limitation in the risk assessment process. Specific algorithms were therefore developed using selected variables affecting pesticide exposure, such as exposure time, use rate, concentration of active ingredient, formulation, number of applications/year, size of the treated area, application machinery, operator's skills, use of personal protective equipment. The exposed subjects were divided in groups (no exposure, low exposure, medium exposure and high exposure). Seventy five percent of the predicted values were found to be consistent with the field data.

Conclusions: Standardized exposure assessment algorithms are essential to provide sound risk assessment. Nevertheless, to generate models which can forecast exposure levels in typical exposure scenarios, field data need to be collected at frequent intervals. In this way a comprehensive database can be established. From such a dataset it is then possible to calibrate and validate robust models. In order to ensure the feasibility of these models, use of validated analytical procedures, including uncertainty measurement, and an effective repeated-measures design, are of utmost importance as well.

48

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIADe Medici D.,
Anniballi F.,
Delibato E.,
Lonati D.,
Locatelli C.,
Fenicia L.In: *Atti del 44th Interagency
Botulism Research
Coordinating Committee
Meeting; Asilomar,
CA (USA), 14-18 Ottobre
2007*; 118.

ITALIAN PROJECT ON INFANT BOTULISM (2007-2009).

Infant Botulism (IB) first recognized in 1976 is an orphan ("rare") disease that affects infants between one and 52 weeks of age. Ingested spores of neurotoxicogenic clostridia can colonize and grow in the large intestine producing botulinum neurotoxins (BoNTs) and causing classical signs and symptoms of botulism. The incidence of IB is low but also underestimated. The illness is difficult to diagnose due the wide spectrum of clinical manifestation and the diagnosis is generally done by physicians with previous personal experience on IB. It is thought that clinical suspicion, correlated with the knowledge of the illness is the principal factor in the diagnosis of IB. The laboratory confirmation of suspected cases needs a rapid and specific method to detect BoNTs producing clostridia in clinical samples. The National Reference Centre for Botulism at the ISS, performs an active surveillance of IB in Italy, with laboratory confirmation of suspected cases. It also performs additional microbiological analysis on clinical and environmental samples, together with the collection of clinical and epidemiological data regarding patients. Twenty-seven cases of IB took place in Italy between 1984 and 2006. These cases occurred in a only few regions where clinicians were already familiar with the illness. After the United States and Argentina, Italy has the third highest number of IB cases. While in the United States IB is already included in National Organization for Rare Disorders, this illness is not yet included in the Italian National Register for rare diseases. In spite of this, a project on infant botulism has been approved and supported by an Italy-USA collaboration project grant on rare diseases. The main objective is to improve knowledge of the disease by training physicians (pediatricians, neurologist and clinical toxicologists) to look out for the possible presence of IB cases and improving public awareness through a prevention program. Standardization of a therapeutic protocol also with specific therapeutic treatment measures will be disseminated. This project will also focused with the aim to include IB in the Italian National Register of Rare Diseases. The project commenced on 1 may 2007 and will involve different aspects of IB and will be structured into WP1, WP2, and WP3. WP1 - The Pavia Poison Control Centre and National Toxicology Information Centre is involved in developing this WP. The main objective is to formulate an educational medical program, to fill the identified information gaps and to improve physician awareness of IB. WP2 - The objective of the WP is to develop rapid molecular biological methods for the detection of BoNTs producing clostridia in clinical samples for the rapid diagnosis of the disease. WP3 - This WP deals with the dissemination of collected data on clinical and microbiological aspects of cases. All the informations will be easily available on the website that can be consulted by all stakeholders.

49

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Fenicia L.,
Anniballi F.,
De Medici D.,
Delibato E.,
Lonati D.,
Locatelli C.

In: *Atti del Workshop
"Rare Diseases and
Orphan Drugs"*; Roma,
7-8 Novembre 2007;
43-44.

RARE DISEASES: INFANT BOTULISM.

Infant Botulism (IB) first recognized in 1976 is an orphan ("rare") disease that affects infants between one and 52 weeks of age. The laboratory confirmation of suspected cases needs a rapid and specific method to detect BoNT producing clostridia in clinical samples. With the exception of the USA, the incidence rate of IB is low, but underestimated. In USA, IB is the most common form of human botulism and about 100 cases are confirmed per year. The "Infant Botulism Treatment and Prevention Program" (IBTPP) in California, provides diagnostic and consultative medical services; and distributes the new orphan drug BabyBIG. The NRCB at the ISS, performs an active surveillance of the disease with laboratory confirmation of suspected cases. Twenty-seven cases of IB occurred in Italy between 1984 and 2006 and the diagnosis is generally done by clinicians familiar with the clinical manifestations and maintaining a very high index of clinical suspicion. After the United States and Argentina, Italy has the third highest number of IB cases. This project, in collaboration also with the California IBTPP is primarily focused on improving IB knowledge and having it included in the Italian National Register of Rare Diseases. The project is structured in three WPs: WP1 - The Pavia Poison Control Centre and National Toxicology Information Centre is involved in developing this WP. The main objective is to formulate an educational medical program, to fill the identified information gaps and to improve physician awareness of IB. WP2 - The objective of the WP is to develop rapid molecular biological methods for the detection of BoNTs producing clostridia in clinical samples for the rapid diagnosis of the disease. WP3 - This WP deals with the dissemination of collected data on clinical and microbiological aspects of cases. All the informations will be easily available on the website that can be consulted by all stakeholders. The preliminary results obtained from this project are: WP1 - A very simple questionnaire sent to European Poison Centers (PCs) with the aim to collect preliminary information concerning epidemiological data, diagnosis and management of botulism disease showed that the IB remains a rare disease. During 2004 to 2006 no cases of IB have been observed in Europe, with the exception of Italy, where 7 cases were diagnosed. Laboratories for analysis exist, but only some are open 24 hours. At present no PCs report having BabyBIG available. WP2 - A multiplex PCR method to detect simultaneously type A,B,E and F BoNTs-genes in fecal samples has been developed and an international European evaluation is in progress. WP3 - A meeting is about to take place with experts of IBTPP in California to discuss items to be incorporated onto the website.

50

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Giampreti A.,
Campilla M.T.,
Guido S.,
Vecchio S.,
Rocchi L.,
Baldi M.L.,
Locatelli C.

In: *Atti del 61° Congresso
Nazionale della Società
Italiana Anestesia
Analgesia Rianimazione
e Terapia Intensiva
(SIAARTI)*; Torino,
18-20 Ottobre 2007;
70; 10: 106.

YOHIMBINE OVERDOSE IN BODY-BUILDER.

Aim: Yohimbine (Yo) is an alkaloid obtained from *Corynanthe Yohimbe* and other biological sources. Yo is clinically applied in the treatment of certain types of erectile impotence. Yo has undergone a resurgence in street use as an aphrodisiac and mild hallucinogen; in the last years Yo is very diffused in body-building community for its hypotized lipolytic and sympaticomimetic effect. We describe a case in which severe acute neurotoxic effects were presented after documented Yo oral ingestion in a bodybuilder.

Case Report: A 37 year-old man after ingestion of estimated 5 grams of Yo and niacin for a body-building competition presented a clinical picture characterized by early generalized malaise, vomiting, loss of consciousness and seizures spontaneously resolved after two minutes. At first evaluation the patient presented GCS 3, and orotracheal intubation and fluids infusion were immediately practised. At admission to the ICU the patient presented: hypertension (acme 259/107 mmHg), tachycardia (acme 140 pulse/minutes) treated with furosemide and labetalol; chest radiographs and brain CT were normal. The patient's history was negative for neurological diseases. An extensive gastric lavage was immediately performed, followed by oral administration of activated charcoal and cathartics. After 12 hours the patient was extubated with normal hemodynamic parameters and neurological examination. The Yo blood levels at about 3, 6, 14 and 22 hours after ingestion were 5240 ng/ml, 2250 ng/ml, 1530 ng/ml, 865 ng/ml respectively. *Conclusion:* Yo utilization in body-building community is a known problem but few data are available about its toxicity and related toxic blood levels. The most common adverse effects from Yo administration include antidiuresis, tachycardia, hypertension, vasodilation, nausea, tremor, irritability, dizziness, headache and hallucinations. In this case report severe hemodynamic, and neurological manifestation are described and a possible correlation with very high levels of Yo blood concentration, in the patient could be evidenced.

51

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIALocatelli C.,
Butera R.,
Lonati D.,
Giampreti A.,
Petroli V.,
Vecchio S.,
Manzo L.In: Atti del
4th Mediterranean
Emergency Medicine
Congress (MEMC);
Sorrento,
15-19 Settembre 2007
(versione elettronica).

RIDUZIONE DELLE REAZIONI AVVERSE DA SOMMINISTRAZIONE DI N-ACETILCISTEINA A DOSE ANTIDOTICA IN FUNZIONE DELLA VELOCITÀ DI INFUSIONE INIZIALE.

La N-acetilcisteina (NAC) è antidoto considerato sicuro anche se durante la somministrazione della dose iniziale è possibile l'insorgenza di effetti avversi (ADR) correlati alla velocità di infusione della dose iniziale. Sono stati studiati tutti i pazienti trattati con NAC a dosi antidotiche in sei mesi per valutare l'incidenza di ADR a NAC. La dose iniziale (150 mg/kg) è stata somministrata per via endovenosa in 90 minuti. ADR sono stati classificati mediante score di gravità. Sono stati analizzati i fattori di rischio per comparsa di ADR, ed i trattamenti farmacologici concomitanti. Sono stati analizzati 40 pazienti, trattati con NAC per intossicazione da paracetamolo (23/40, 57.5%), da solventi (13/40, 32.5%), o per altra patologia da causa tossica (4/40, 10%). Tra i fattori di rischio analizzati, è stato registrato 1 caso di asma bronchiale; 4 pazienti risultavano in trattamento con antiistaminici anti-H2, e 9 con antiinfiammatori e/o cortisonici. Eventi avversi a NAC sono stati osservati in un solo caso (1/40, 2.5%). Analizzando il solo gruppo di pazienti senza trattamenti farmacologici concomitanti l'incidenza ADR a NAC è stata del 3.7% (1/27). La reazione è stata di lieve entità (flushing), non ha richiesto terapia specifica e non ha comportato la sospensione del trattamento antidotico. I protocolli standard prevedono la somministrazione della dose iniziale di NAC in 15-30 minuti. Tale velocità di infusione è associata ad un'incidenza di ADR che negli studi retrospettivi varia tra il 5.3 e l'11%, e risulta 3 volte superiore nei soggetti asmatici. Due studi prospettici hanno documentato che la riduzione della velocità di infusione della dose iniziale da 15 a 60 minuti comporta una diminuzione dell'incidenza di ADR dal 56.0% al 19.6%. I risultati del nostro studio confermano queste osservazioni e suggeriscono che l'ulteriore riduzione della velocità di infusione della dose iniziale, somministrata in 90 minuti, sia associata a un'incidenza di effetti avversi ancora minore.

52

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIALocatelli C.,
Coccini T.,
Butera R.,
Petroli V.,
Lonati D.,
Giampreti A.,
Manzo L.In: Atti del 44th Congress
of the European
Societies of Toxicology
(EUROTOX); Amsterdam
(The Netherlands),
7-10 Ottobre 2007;
172; 35.

DIAGNOSTIC EFFICACY OF URINARY AMANITIN ANALYSIS IN MUSHROOM POISONING.

Background: Urinary amanitin analysis (AMA-u) may be a valuable tool in the early diagnosis of mushroom poisoning; a cut-off of 5 ng/ml showed high sensitivity and specificity in patients sampled within 36 hours after mushroom ingestion.

Purpose: To determine sensitivity, specificity, positive and negative predictive values, and diagnostic efficacy of AMA-u in a cohort of patients of suspected mushroom poisoning prospectively studied.

Methods: All cases of wild mushroom ingestion with gastrointestinal symptoms presenting in the Emergency Departments in the period September-December, 2002 were analyzed. Definitive diagnosis was considered the gold standard. Urine samples were collected between 3.8 and 69.5 hours (mean 18.1±14.1) after mushroom ingestion. AMA-u were performed with Amanitin ELISA Kit (Bühlmann-Laboratories, CH).

Results: One hundred and sixty-two patients were included in the study. Definitive diagnosis of amatoxin-containing mushroom poisoning was made in 38 cases (23.5%). Diagnostic performance of initial clinical assessment (ICA) made by a trained toxicologist and AMA-u were compared. AMA-u result disagreed with ICA in 21.1-24.1% of cases (according to the cut-off chosen, from 1.5 to 10.0 ng/ml), and modified the diagnosis in 13.6% of cases.

Conclusions: The disagreement observed in a significant proportion of cases between ICA and AMA-u documents the diagnostic efficacy of this analytical investigation. In patients in whom the ingestion of amatoxin containing mushrooms is suspected or can not be excluded, AMA-u may be helpful to identify patients with benign illnesses: this would avoid unnecessary treatments, or allow discontinuing them. In this regard, the timely availability of the analysis is crucial.

53**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIALocatelli C.,
Giampreti A.,
Lonati D.,
Petrolini V.,
Vecchio S.,
Manzo L.*In: Atti del 61° Congresso
Nazionale della Società
Italiana Anestesia
Analgesia Rianimazione
e Terapia Intensiva
(SIAARTI); Torino,
18-20 Ottobre 2007; 73.***CLINICAL EVOLUTION AND ANTIDOTIC TREATMENT OF 228 VIPER-BITTEN PATIENTS.**

The objective is to describe the clinical worsening of Vipera-bitten patients in order to identify a correlation between clinical gradation at admission and evolution of clinical course, and between these parameters and antidotic treatment (Fab). Furthermore, to compare Fab prescription released by the Pavia Poison Centre (PPC) in two different periods. All cases of Vipera bites referred to PPC over 2002, 2005 and 2006 (79, 76 and 73 cases) were studied. Patients were evaluated for grading at admission and during clinical course (Grading-Severity-Score - GSS), and for overall management. Fab prescription was evaluated comparing 2002 vs 2006. 228 Vipera-bitten patients were included: at PPC first evaluation, 132 (57%) patients presented fang marks only (GSS0), 77 (34%) local edema (GSS1), 18 (8%) regional edema and/or mild systemic manifestations (GSS2), 1 (1%) severe local and systemic manifestations (GSS3). 45 cases were lost at follow-up. Among GSS0-patients, dry-bite was assessed in 92/107 cases, whereas 15/107 patients (14%) evolved in local signs (GSS1), 6 presented also mild systemic effects (GSS2) and 3 required antivenom. All of the 60 GSS1 developed worsening of edema, 23 (38%) presented also systemic symptoms and 10 needed antivenom. 15/15 GSS2 evolved with severe local symptoms, and 12/15 with severe systemic symptoms; 9 cases (60%) required Fab. Worsening was observed in 14% of GSS0 and in 82% of GSS1 during the first 12 hours; the severity of envenomation increased in 80% of GSS2 during the following 24 hours. The total number of envenomated patients was 91, Fab was needed in 28 (30.7%); no fatal cases were reported. The comparison between 2002 and 2006 demonstrates an increase in Fab prescription by toxicologists: from 50 to 66% of GSS0-presenting-patients and from 60 to 86% of GSS2-presenting-patients. Despite the high percentage of dry-bites, some GSS0-patients worsen and require antidote: observation of at least 12 hours is advisable for a correct management in all cases. The absence of fatal cases can be related to prompt Fab prescription by toxicologist during assiduous follow-up necessary to properly evaluate the clinical course.

54**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIALocatelli C.,
Lonati D.,
Fenicia L.,
Anniballi F.,
Petrolini V.,
Giampreti A.,
Vecchio S.,
Butera R.,
Manzo L.*In: Atti del 44th Congress
of the European
Societies of Toxicology
(EUROTOX); Amsterdam
(The Netherlands),
7-10 Ottobre 2007;
S135-S136.***POISON CENTRE INVOLVEMENT IN THE DIAGNOSIS AND TREATMENT OF FOODBORNE BOTULISM.**

Foodborne-botulism (FBo) is a rare poisoning that can represent a medical and public health emergency: 276 cases (12 fatal) of FBo have been laboratory-confirmed in Italy (years 1984-2006) by the National Reference Centre for Botulism (NRCB).

Purpose: To evaluate the incidence and the clinical characteristic of FBo-cases registered in 2005 by the Pavia Poison Centre (PPC).

Methods: Retrospective analysis of FBo-cases referred to PPC and evaluation of incidence, presence of typical syndrome, and efficacy/safety of the antidotic treatment.

Results: Among the 2005 PPC cases, 2195 (9.45%) were related to a suspected food-poisoning. In 37 cases a possible contaminated food was ingested, and 12 of these (age: 9 month-65 year) presented a clinical diagnosis of probable FBo: in 6 patients NRCB analysis confirmed the clinical diagnosis. In nine cases the contaminated food was identified by epidemiological criteria or laboratory analysis. Time of hospital presentation, clinical course and severity differed among patients. Dry mouth, diplopia, ptosis, dysarthria were the most common presentation symptoms. Seven (7/12) cases evolved with a typical descendent paralysis and needed prolonged mechanical ventilation; in nine (9/12) cases trivalent-antitoxin-ABE was administered, without adverse reactions. Ten cases recovered completely in 1-8 month period, and two patients died.

Conclusions: FBo clinical diagnosis can be difficult and may require a toxicological consultation. The optimal antitoxin dose needs to be established in the single case. The Poison Centre represents a clinical and epidemiological point of reference for prompt diagnosis and early management of poisoned patients, such as in the surveillance of possible outbreaks.

55

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Locatelli C.,
Lonati D.,
Giampreti A.,
Petrolini V.,
Butera R.,
Manzo L.

In: *Atti del XXVII International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT); Atene (Grecia), 1-4 Maggio 2007; 45; 381.*

ACCIDENTAL PARAQUAT POISONING: A SEVERE CASE WITH SUCCESSFUL MANAGEMENT.

Objective: Paraquat (P) poisoning is a potentially serious event that could require, in the absence of a specific antidotal treatment, the use of invasive procedures and aggressive pharmacological therapies. Among 218 cases of exposure to pesticides referred to Pavia Poison Control Centre over a 5-month period in 2005, 5 (2.3%) were of P exposure. Among these, 2 were fatal voluntary ingestions and 2 accidental non toxic exposures: we describe the fifth case in which all the available treatments were applied.

Case Report: A 46-year-old man affected by chronic obstructive bronchopneumopathy (COPD) was admitted to emergency room 1.5 hour after accidental ingestion of about 80 ml of a 11.7% P and 5.9% diquat solution. At admission the patient was asymptomatic; neither pharyngodinia nor vomiting was reported. Arterial blood pressure and gas analysis were normal. Gastric lavage, activated charcoal and cathartics were immediately practised. Fuller's earth solution every 2 hours for one day, forced diuresis, N-acetylcysteine (NAC, 150 mg/kg i.v. followed by 300 mg/kg/day for 10 days), and vitamin C (4 g/day for 15 days) were promptly administered. P blood level at 8 hours after ingestion was 1.9 mg/L, so three charcoal hemoperfusion (HPC) sessions were carried out. At the end of HPC, a pulsed cyclophosphamide-methylprednisolone therapy (cyclophosphamide 15 mg/kg/day for 2 days and methylprednisolone 1g/day for 3 days) was started. Vitamin E (600 mg/day for 30 days) was started by day 4. P blood levels at day 4 and 8 results were undetectable. Pulmonary function tests, gas analysis, and chest radiographs during hospitalization were compatible with the patient's disease (COPD). The patient remained always asymptomatic and was discharged at day 15 with dexamethasone 30 mg/day for 45 days, followed by 12 mg/day for 3 months. At follow-up, pulmonary and liver function tests, gas analysis (repeated one time a week up to 3 months after discharging) and repeated chest radiographs resulted without abnormalities: at 8 months the patient's follow-up was stopped.

Conclusion: P poisoning is often associated with a dramatic clinical course. HPC can reduce P plasma level and NAC, antioxidants and corticosteroids, especially combined with cyclophosphamide may offer some benefits by preventing oxidative damage and pulmonary fibrosis. In this case, the mortality rate related with patient's plasma level was about 80-90% (1); early diagnosis, decontamination and subsequent treatment may have played a discriminant role for the successful management.

Reference: 1. Proudfoot AT, Stewart MS, Levitt T, et al. Paraquat poisoning: significance of plasma-paraquat concentrations. *Lancet* 1979; i: 330-332.

56

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Locatelli C.,
Lonati D.,
Giampreti A.,
Petrolini V.,
Butera R.,
Manzo L.

In: *Atti del XXVII International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT); Atene (Grecia), 1-4 Maggio 2007; 45; 359.*

EVOLUTION OF CLINICAL FEATURES AND MANAGEMENT OF 228 VIPER-BITTEN PATIENTS IN ITALY.

Objective: To describe the clinical course of Vipera-bitten patients in Italy in order to identify a correlation between clinical gradation at admission and evolution/severity of clinical course, and between these two parameters and antidotal treatment (Fab). Furthermore, to compare Fab prescription released by the Pavia Poison Centre (PPC) in two different periods of time.

Methods: All cases of Vipera bites referred to PPC over 2002, 2005, and 2006 (79, 76 and 73 cases, respectively) were retrospectively studied. Patients were evaluated for clinical grading at admission and during clinical course according to the Grading-Severity-Score (GSS) (1), and for overall management. Fab prescription was evaluated comparing the first and last year studied (2002 vs 2006).

Results: 228 Vipera-bitten patients were included: at PPC first evaluation, 132 (57.9%) patients presented with fang marks only (GSS0), 77 (33.8%) with local edema (GSS1), 18 (7.9%) with regional edema and/or mild systemic manifestations (GSS2), 1 (0.4%) with severe local and systemic manifestations (GSS3). Among GSS0-patients, dry-bite was assessed in 92/107 cases (85%), whereas 15/107 patients (14%) had local signs (GSS1) and 3 presented also mild systemic effects (GSS2), requiring antivenom. All of the 60 GSS1-patients developed worsening of local edema, 11 (18.3%) presented also systemic symptoms; 12 patient of this group needed antivenom. 15/15 GSS2-patients evolved with severe local symptoms, and 12/15 with severe systemic symptoms; Fab was required in 12 cases (80%). Worsening of clinical picture was observed in 14% of GSS0 and in 82% of GSS1-patients during the first 12 hours; the severity of envenomation increased in 80% of GSS2-patients during the following 24 hours. The total number of envenomed patients (excluding the 45 drop-outs and the dry-bites) was 91, Fab was needed in 28 (30.7%); no fatal cases were reported. The comparison between 2002 and 2006 demonstrates an increase in Fab prescription by toxicologists: from 20 to 40% of GSS0-presenting-patients and from 75 to 100% of GSS2-presenting-patients, whereas no differences appear between GSS1-presenting-patients (20 vs. 21%).

Conclusions: Viper bite is a potentially serious event that requires immediate hospital care and toxicological evaluation. Despite the high percentage of dry-bites, some GSS0-patients worsen and require antidote: observation of at least 12 hours is advisable for a correct management in all cases. The absence of fatal cases can be related to prompt Fab prescription by toxicologist during assiduous follow-up necessary to properly evaluate the clinical course.

References: 1. Audebert F, Sorkine M, Robbe-Vincent A, Cassian B. Human and Experimental Toxicology 1994; 13: 683-688.

57

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIALocatelli C.,
Lonati D.,
Giampreti A.,
Petrolini V.,
Manzo L.In: Atti del
4th Mediterranean
Emergency Medicine
Congress (MEMC);
Sorrento,
15-19 Settembre 2007
(versione elettronica).

SODIUM CHLORATE SELF-POISONING: A FATAL CASE.

Background: Chlorate salts (Ch-s) poisoning has a high mortality rate and requires prompt treatment. The main mechanism of toxicity of Ch-s relates to the strong oxidative action on all cells and tissues (erythrocyte cell membrane and haemoglobin), which causes massive haemolysis, methaemoglobinemia (metHb), disseminated intravascular coagulation and acute renal failure.

Case: A 28-year-old man was admitted to the emergency department (ED) 1.5 hour after voluntary ingestion of unknown amount of the Radical® herbicide (sodium-chlorate 38%). At admission, the patient referred only diarrhea. The first laboratory investigations and blood gas-analysis were normal. An extensive gastric lavage was performed, followed by activated charcoal and magnesium sulphate administration. Subcyanosis and then massive cyanosis with metHb 54.4%, trismus and respiratory arrest (requiring mechanical ventilation) progressively appeared in 90 minutes. Three hours later the clinical course was characterized by hypotension (requiring fluids and sympathomimetics), rhabdomyolysis, massive haemolysis, renal failure, metabolic acidosis, coagulation disorders and cardiac tissue hypoxia: metHb reached 81%. Intravenous high dose sodium bicarbonate was administered to treat the metabolic acidosis and rhabdomyolysis. Antidote treatment with methylene-blue and Na-thiosulfate, associated with 3 exchange-transfusion sessions combined with continuous haemodialysis, fresh frozen plasma and blood transfusion were given. Despite this, the patient died 20 hours after admission.

Discussion: Ch-s poisoning is a potentially fatal event in which diarrhoea can be the only symptom at presentation. Cyanosis and metHb are specific signs of poisoning, as chlorate chromatographic analysis is unavailable in EDs. Massive haemolysis, coagulation dysfunction, renal failure and cardiovascular collapse complicate the clinical course. Methylene-blue can reduce metHb to haemoglobin in the first phase, but its efficacy can be limited by Ch-s inactivation of glucose-6-phosphate-dehydrogenase, or by the presence of haemolysis; Na-thiosulfate may inactivate the chlorate-ion, but its use is controversial.

58

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIALocatelli C.,
Lonati D.,
Giampreti A.,
Petrolini V.,
Vecchio S.,
Butera R.,
Manzo L.In: Atti del 61° Congresso
Nazionale della Società
Italiana Anestesia
Analgesia Rianimazione
e Terapia Intensiva
(SIAARTI); Torino,
18-20 Ottobre 2007;
73; 10: 107.

XILOL ACUTE TOXICITY AFTER SECONDARY EXPOSURE TO XILOL-MALATHION MIXTURE IN THE EMERGENCY DEPARTMENT.

Introduction and Objectives: Emergency Department (ED) staff caring for pesticide-contaminated patients is at risk for developing toxicity from secondary contamination. To recognise the nature of the causative agent is necessary for appropriateness of treatment and follow-up.

Materials and Methods: Health-care workers suffering from secondary exposure to chemicals in the ED were studied. The source of exposure was a patient admitted to ED after a large malathion-xilol (80-20%, respectively) mixture ingestion in suicidal attempt. Despite appropriate care, the patient died in the ED 45 minutes after the admission, and the body was left in a ED room for 2 hours. A large amount of ingested product was vomited (approximately 650 ml), and the smell of chemicals was relevant. Health-care workers did not wear appropriate respiratory or skin protective equipment while caring for the patient nor while the body remained in the ED. Clinical data and plasma pseudocholinesterase (pChE) levels were recorded and evaluated. A questionnaire was given to health-care workers in order to obtain information about health professional category, location in the ED, contact with the contaminated patient, onset and duration of symptoms if any. pChE levels were measured at the end of exposure and then re-measured after a mean interval of 4,7 hours (range: 4-7 hours). *Results:* Fifteen health-care workers were on duty when the poisoned patient was admitted to the ED: two were physicians, twelve were nurses and one was an undertaker's technician. Ten people stood in the same room with the contaminated patient, two worked in the next room and three were somewhere else in the ED. Eight subjects cared or moved the patient. Fourteen health-care workers (93,3%) were symptomatic and only one was asymptomatic. The most frequently reported symptoms were eye irritation (11 cases), pharyngodynia (7 cases), nausea (6 cases), lacrimation (5 cases), headache (4 cases), cough (4 cases) and excessive salivation (2 cases). Symptoms began during the exposure and lasted for several hours. Mean pChE levels (reference values: 3500-11000 UI/l) were 7620±1592 UI/l (range: 4400-10300 UI/l) at the end of the exposure and 7580±1790 UI/l (range: 4400-11400 UI/l) in the following control.

Conclusion: Secondary exposure affected both health-care workers who cared the contaminated patient, and those who did not. Diagnostic reduction in pChE levels was not observed, suggesting that signs and symptoms in health-care workers were related to the inhalation of the more volatile compound xilol, estimated to be in concentration of approximately 200 ppm in the ED environment.

59

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIALocatelli C.,
Lonati D.,
Petrolini V.,
Giampreti A.,
Butera R.,
Fenicia L.,
Anniballi F.,
Manzo L.In: *Atti del 1^{er} Congrès de la Société Française de Médecine d'Urgence; Parigi (Francia), 30 Maggio - 1 Giugno 2007; Journal Européen des Urgences (JEUR); 2007; 20; 1: S166.*

BOTULISME ISSU DES ALIMENTS EN ITALIE: EXPÉRIENCE D'UNE ANNÉE AU CENTRE ANTIPOISON DE PAVIE.

Le botulisme (Bo) est une émergence médicale et de santé publique. Le diagnostic tempestif et le traitement précoce sont essentiels afin de minimiser les risques de mort. En Italie, le botulisme issu de produits alimentaires (FBo) est la forme la plus fréquente. Depuis 1984, 267 cas (6 mortels) de FBo ont été confirmés au laboratoire par le Centre National de Référence pour le Botulisme (CNRB).

Objectif: Analyser tout les cas de Bo et FBo référés au Centre Antipoison de Pavie (PC).

Méthodes: Une analyse rétrospective de tous les cas d'empoisonnement au Bo référés au PC en 2005 a été faite pour évaluer: (i) incidence; (ii) concordance entre symptômes et syndrome typique; (iii) efficacité et sécurité du traitement antidote. Résultats: sur 37 cas, un probable aliment contaminé a été ingéré, et sur 12 d'entre eux (inclus dans l'étude) un diagnostic clinique de FBo a été établi. Trois groupes ont été observés, et dans 9 cas, l'aliment contaminé a été identifié par critère épidémiologique et/ou analyse de laboratoire. Le temps de présentation à l'hôpital et l'évolution clinique des patients (9 mois- 65 ans) étaient différents dans tous les cas. Bouche sèche, diplopie, ptose bilatérale, dysarthrie, étaient les symptômes plus fréquents à la présentation; 7 cas ont évolué par une paralysie descendante typique et ont eu besoin de ventilation mécanique prolongée; sur 9 cas, l'antitoxine ABE a été administrée, sans réactions adverses; sur 6 cas, l'analyse du CNRB a confirmé le diagnostic. 2 cas ont résulté du type FBo. 11 cas ont récupérés complètement en 1-8 mois: 1 cas fatal a été enregistré.

Conclusion: Bo est une pathologie rare dans laquelle le correct diagnostic rapide est difficile et peut demander une consultation toxicologique. PC représente un point de référence clinique et épidémiologique pour le Bo: les cas de cette étude représentent 80% de tous les cas italiens recensés en 2005. L'activité du PC est essentielle pour le diagnostic et le traitement des patients empoisonnés, et pour l'identification et la surveillance des manifestations. Pour améliorer le diagnostic de Bo, un test rapide se révèle nécessaire. La dose anti-toxine optimale doit être établie dans chaque cas.

60

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIALocatelli C.,
Petrolini V.,
Butera R.,
Lonati D.,
Giampreti A.,
Vecchio S.,
Manzo L.In: *Atti del 44th Congress of the European Societies of Toxicology (EUROTOX); Amsterdam (The Netherlands), 7-10 Ottobre 2007; 176; S136.*

ANTIDOTES STOCKPILES AND TOXICOLOGICAL PROCEDURES IN CHEMICAL INDUSTRIES: A UNIQUE OPERATING SYSTEM FOR SPECIFIC ANTIDOTE AVAILABILITY AND PROPER INTERVENTION IN CHEMICAL EMERGENCIES.

Acute occupational poisonings usually involve several victims, with subsequent need of large amount of antidotes; however, hospitals have, generally, insufficient antidotes stockpiles.

Purpose: To create an operating system to ensure prompt antidote availability for toxicologic emergencies in industrial setting, through the constitution of antidotes stockpiles in chemical plants combined with the toxicologic-guided intervention guaranteed by a specifically structured Poison Centre (PC).

Methods: The study included 44 petrochemical, pharmaceutical/chemical plants. Working processes were analyzed in order to identify chemicals potentially involved and risks of acute poisoning. Accidental non-occupational poisoning occurring at the workplace was also considered. Potential antidote use was assessed, according to factory size and workers number. Operating procedures to ensure the proper use of antidotes were prepared.

Results: Each plant received non-specific antidotes (e.g. activated charcoal, simethicone, liquid-paraffin), antidotes for fire victims management (amyl-nitrite, oxygen, hydroxocobalamin), and other antidotes (folic-acid, ethanol, methylene-blue, calcium-salts, calcium-disodium-edetate, N-acetyl-cysteine, polyethylene-glycol-400, penicillamine, sodium-thiosulfate) supplied according to plant's specific risks. Antidote stocking and replacement is a PC responsibility, and in order to avoid misuse, antidotes have to be used under the PC physician advice and supplied to the hospital emergency departments along the poisoned patients. During the first 10 years of activity, the recourse to industrial antidotes stockpiles occurred several times.

Conclusions: Insufficient antidotes hospital stocking is a worldwide problem. This unique procedure for the management of antidotes stockpiles in industrial plants under the PC responsibility, together with clinical advice from PC physicians, should allow a timely and proper management of cases of acute occupational poisoning.

61

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Locatelli C.,
Petroli V.,
Lonati D.,
Giampreti A.,
Vecchio S.,
Bigi S.,
Manzo L.

In: Atti del
4th Mediterranean
Emergency Medicine
Congress (MEMC);
Sorrento,
15-19 Settembre 2007
(versione elettronica).

CLINICAL WORSENING AND ANTIDOTIC TREATMENT OF 228 VIPER-BITTEN PATIENTS IN ITALY.

Introduction: The objectives are to: (1) describe the clinical worsening of Vipera-bitten patients in order to identify a correlation between clinical gradation at admission and evolution of clinical course, and between these parameters and antidote treatment (Fab), and (2) to compare Fab prescription by the Pavia Poison Centre (PPC) in two different periods.

Methods: All cases of Vipera bites referred to PPC over 2002, 2005 and 2006 (79, 76 and 73 cases) were studied. Patients (pts) were evaluated for grading at admission and during clinical course (Grading-Severity-Score - GSS), and for overall management. Fab prescription was evaluated comparing 2002 vs 2006.

Results: 228 Vipera-bitten pts were included: at PPC first evaluation, 132 (57%) pts presented fang marks only (GSS0), 77 (34%) local edema (GSS1), 18 (8%) regional edema and/or mild systemic manifestations (GSS2), 1 severe local and systemic manifestations (GSS3). 45 cases were lost at follow-up. Among GSS0-pts, dry-bite was assessed in 92/107 cases, whereas 15 pts (14%) evolved in local signs (GSS1), 6 presented also mild systemic effects (GSS2) and 3 required antivenom. All of the 60 GSS1 developed worsening of edema, 23 (38%) presented also systemic symptoms and 10 needed antivenom. 15/15 GSS2 evolved with severe local symptoms, and 12 with severe systemic symptoms; 9 cases (60%) required Fab. Worsening was observed in 14% of GSS0 and in 82% of GSS1 during the first 12 hours; the severity of envenomation increased in 80% of GSS2 during the following 24 hours. The total number of envenomated pts was 91, Fab was needed in 28 (30.7%); no fatal cases were reported. The comparison between 2002 and 2006 demonstrates an increase in Fab prescription by toxicologists: from 50 to 66% of GSS0-presenting- pts and from 60 to 86% of GSS2- presenting-pts.

Conclusions: Despite the high percentage of dry-bites, some GSS0-pts worsen and require antidote: observation of at least 12 hours is advisable for a correct management in all cases. The absence of fatal cases can be related to prompt Fab prescription by toxicologists during assiduous follow-up necessary to properly evaluate the clinical course.

62

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Locatelli C.,
Petroli V.,
Lonati D.,
Papa P.,
Rocchi L.,
Valli A.,
Butera R.,
Manzo L.

In: Atti del 1^{er} Congrès
de la Société Française
de Médecine d'Urgence;
Parigi (Francia),
30 Maggio - 1 Giugno 2007;
Journal Européen
des Urgences (JEUR);
2007; 20; 1: S165.

EVALUATION DU BESOIN DE TEST DE LABORATOIRE ET DE TRAITEMENT ANTIDOTE DANS LA GESTION D'EMPOISONNEMENT SUSPECT AU GLYCOL ÉTHYLÈNE/MÉTHANOL.

Introduction: Les directives pour l'empoisonnement au glycol éthylène (GE) /méthanol (M) suggèrent que le traitement antidote doit être basé sur "l'anamnèse", le niveau sérique de GE /M, le gap osmolaire et l'acidose métabolique (AM). En Italie, l'analyse de GE/M est faite (24 heures/jour) par peu de laboratoires, et le gap osmolaire n'est pas disponible dans les services d'urgence.

Objectif: évaluer la pertinence des critères utilisés pour commencer le traitement antidote chez les patients ayant ingéré GE/M.

Matériels et Méthodes: Une analyse rétrospective de 2 ans sur les expositions à GE/M référés au Centre Anti-Poison a été faite: l'anamnèse, la présentation clinique, la présence de MA, les niveaux sériques de GE/M et le traitement antidote ont été évalués.

Résultats: Soixante deux cas (GE,57; M,5) ont été inclus dans l'étude. Vingt quatre patients (38,7%) ont été considérés non à risque (petite quantité ingérée). Sur 38 patients (61,3%) avec une exposition potentiellement toxique, 23 (23/38, 61%) ont été évalués comme risque léger-moderé (quantité ingérée 0,5 ± 0,4 ml/kg) et n'ont pas nécessités de traitement antidote: aucun de ces patients n'a montré AM et dans le sérum de 6 cas, les niveaux de GE/M détectés étaient < 20 mg/dl (à 4,4 ± 1,1 heures). Dans les 15 cas restants (15/38, 39%) la quantité ingérée (1,2 ± 1,0 ml/kg) et /ou les résultats cliniques étaient suggestifs d'empoisonnement nécessitant un traitement antidote: les niveaux de GE/M obtenus 14,2 ± 18,5 heures après prélèvement ont permis la discontinuation du traitement évitable dans 10 cas, et ont confirmé la nécessité de traitement ultérieur chez 5 patients.

Discussion et Conclusion: La disponibilité de dosage GE/M à tout moment pourrait permettre de différencier les patients avec ou sans exposition toxique, afin d'éviter les traitements inutiles, et d'identifier les cas dans lesquels l'hospitalisation, la surveillance de AM et le traitement antidote est nécessaire.

63

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIALonati D.,
Giampreti A.,
Petrolini V.,
Vecchio S.,
Locatelli C.,
Butera R.,
Manzo L.*In: Atti del 61° Congresso Nazionale della Società Italiana Anestesia Analgesia Rianimazione e Terapia Intensiva (SIAARTI); Torino, 18-20 Ottobre 2007; 73; 10: 106-107.*

RIDUZIONE DELLE REAZIONI AVVERSE DA SOMMINISTRAZIONE DI N-ACETILCISTEINA A DOSE ANTIDOTICA IN FUNZIONE DELLA VELOCITÀ DI INFUSIONE INIZIALE.

La N-acetilcisteina (NAC) è antidoto considerato sicuro anche se durante la somministrazione della dose iniziale è possibile l'insorgenza di effetti avversi (ADR) correlati alla velocità di infusione della dose iniziale. Sono stati studiati tutti i pazienti trattati con NAC a dosi antidotiche in sei mesi per valutare l'incidenza di ADR a NAC. La dose iniziale (150 mg/kg) è stata somministrata per via endovenosa in 90 minuti. ADR sono stati classificati mediante score di gravità. Sono stati analizzati i fattori di rischio per comparsa di ADR, ed i trattamenti farmacologici concomitanti. Sono stati analizzati 40 pazienti, trattati con NAC per intossicazione da paracetamolo (23/40, 57.5%), da solventi (13/40, 32.5%), o per altra patologia da causa tossica (4/40, 10%). Tra i fattori di rischio analizzati, è stato registrato 1 caso di asma bronchiale; 4 pazienti risultavano in trattamento con antiistaminici anti-H2, e 9 con antiinfiammatori e/o cortisonici. Eventi avversi a NAC sono stati osservati in un solo caso (1/40, 2.5%). Analizzando il solo gruppo di pazienti senza trattamenti farmacologici concomitanti l'incidenza ADR a NAC è stata del 3.7% (1/27). La reazione è stata di lieve entità (flushing), non ha richiesto terapia specifica e non ha comportato la sospensione del trattamento antidotico. I protocolli standard prevedono la somministrazione della dose iniziale di NAC in 15-30 minuti. Tale velocità di infusione è associata ad un'incidenza di ADR che negli studi retrospettivi varia tra il 5.3 e l'11%, e risulta 3 volte superiore nei soggetti asmatici. Due studi prospettici hanno documentato che la riduzione della velocità di infusione della dose iniziale da 15 a 60 minuti comporta una diminuzione dell'incidenza di ADR dal 56.0% al 19.6%. I risultati del nostro studio confermano queste osservazioni e suggeriscono che l'ulteriore riduzione della velocità di infusione della dose iniziale, somministrata in 90 minuti, sia associata a un'incidenza di effetti avversi ancora minore.

64

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIALonati D.,
Locatelli C.,
Petrolini V.,
Giampreti A.,
Fenicia L.,
Anniballi F.,
Butera R.,
Manzo L.*In: Atti del XXVII International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT); Atene (Grecia), 1-4 Maggio 2007.*

FOODBORNE BOTULISM IN ITALY: THE PAVIA POISON CENTRE CASES IN 2005.

Introduction: Botulism (Bo) can be a medical and public health emergency, and prompt diagnosis and early treatment are essential. In Italy, foodborne botulism (FBo) is the most frequent form; from 1984 to 2005, 267 cases of FBo (eleven of which fatal) have been laboratory confirmed at the National Reference Centre for Botulism (NRCB), Istituto Superiore di Sanità, Rome.

Objective: To analyze all cases of Bo referred to Pavia Poison Control Centre (PCC).

Methods: A retrospective analysis of all cases of Bo referred to PCC in the year 2005 was performed to evaluate (i) incidence of Bo, (ii) concordance between symptoms and typical syndrome, and (iii) indication, use, efficacy and safety of the antidote treatment.

Results: In 37 cases, a possible contaminated food was ingested; in 12 of these (12/37; 32.5%), the clinical diagnosis of FBo was made by the toxicologist, and were included in this study. Three outbreaks were observed, and in 9 cases (9/12) the contaminated food was identified by epidemiological criteria and/or laboratory analysis. Time of hospital presentation and clinical course of poisoned patient (age: 9 months - 65 years) were different in all cases. Dry mouth, diplopia, bilateral ptosis, and dysarthria were the most common symptoms at presentation; seven cases (7/12) evolved with a typical descendent paralysis and needed prolonged mechanical ventilation; in nine cases (9/12) antidote (trivalent antitoxin ABE) was administered, without adverse reactions; and in six cases (6/12) laboratory analysis performed by NRCB confirmed clinical diagnosis. For the first time in Italy, two cases resulted of type F botulism and were unresponsive to antidotal treatment with trivalent antitoxin started before the identification of the toxin-type. Eleven cases (11/12) recovered completely in a variable time (1-8 months): one fatal case was reported.

Conclusion: Bo is a rare disease in which early and accurate diagnosis is difficult and may require a toxicological consultation. The poison centre represents a clinical and epidemiological point of reference for Bo: the cases of this study represent the 80% of the all assessed Italian cases in 2005. So, the PCC support is essential for the diagnosis and the management of poisoned patients (e.g., specific laboratory tests, antidotal treatment), and in the identification and surveillance of possible outbreaks. To ameliorate the diagnosis of Bo a rapid test should be necessary. The optimal antitoxin dose needs to be established in the single case.

65**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIALonati D.,
Locatelli C.,
Petroli V.,
Giampreti A.,
Vecchio S.,
Manzo L.*In: Atti del 5° Congresso Nazionale della Società Italiana di Anestesia, Rianimazione, Emergenza e Dolore (SIARED); Napoli, 20-22 Settembre 2007; 114-124.***L'INTERVENTO SANITARIO NELLE MAXIEMERGENZE CHIMICHE. ASPETTI ORGANIZZATIVI, DIAGNOSTICI, TERAPEUTICI E APPLICAZIONE DI MEZZI DI TELEMEDICINA.**

Parallelamente al progresso, si assiste a un aumento dei rischi legati agli incidenti tecnologici rispetto a quelli naturali. Tali rischi hanno assunto, nell'ultimo secolo, connotati nuovi legati alla produzione e all'utilizzo di un numero notevole di sostanze chimiche. I rischi tecnologici maggiori (industrie petrolchimiche e nucleari, trasporti di materiali pericolosi) tendono a svilupparsi più rapidamente delle misure preventive, e la vulnerabilità delle popolazioni, specie con l'inurbamento, aumenta. Le catastrofi tossicologiche possono essere conseguenza di molteplici cause, non sempre prevedibili, e pertanto non è possibile "abbassare la guardia" nonostante gli impegni profusi in campo preventivo. Di fatto, la nostra civiltà ha probabilmente prodotto dei rischi prima di essere in grado di affrontarli e, paradossalmente, per ciò che concerne la capacità di intervento negli incidenti, sono spesso più noti e affrontabili i rischi prodotti da eventi naturali incontrollabili e inevitabili rispetto a quelli prodotti dall'uomo, dei quali egli stesso non conosce perfettamente gli effetti. La gestione ottimale del soccorso sanitario in caso di catastrofe tossicologica richiede interventi precisi e coordinati da parte di numerose forze che intervengono nelle situazioni di emergenza. Per un intervento efficace è quindi necessario predisporre piani specifici nei quali vengano opportunamente definiti i ruoli e i compiti di tutte le figure previste, i mezzi necessari e disponibili, le modalità di coordinamento. Questi piani devono essere ben noti tanto alle forze e strutture istituzionali per l'emergenza che intervengono in caso di incidente chimico, quanto a coloro che possono essere chiamati a intervenire per le proprie competenze. Anche i sistemi informatici e telematici oggi disponibili possono essere applicati nella gestione del soccorso sanitario per le urgenze ed emergenze tossicologiche. I benefici della telematica sono particolarmente evidenti per l'assistenza sanitaria in caso di incidente chimico di ampie dimensioni che comporti un improvviso e imprevedibile squilibrio fra risorse assistenziali e bisogni delle vittime e della collettività. Nelle emergenze tossicologiche tale squilibrio è aggravato dalla scarsa disponibilità di competenze specialistiche nel territorio. In tali situazioni, la telemedicina può migliorare l'efficacia e la tempestività del soccorso sanitario e le capacità operative delle strutture ospedaliere periferiche, specie nelle zone decentrate. I contatti telematici adottati dal CNIT si sono rivelati idonei per l'attività di consultazione a distanza e per mantenere i collegamenti tra il Centro, gli ospedali e le altre strutture intervenute nella gestione locale dell'emergenza, permettendo al tossicologo del Centro Antiveneni una veloce comprensione dell'evento; le condizioni dei pazienti sono rapidamente apprezzate grazie alla trasmissione di immagini che integrano le descrizioni verbali. Un modello ottimale per l'intervento in caso di incidenti chimici, pertanto, potrebbe risultare dall'integrazione dei piani di intervento dell'industria con quelli dei servizi sanitari deputati alla gestione delle urgenze ed emergenze e di un Centro Antiveneni specialistico, verificandone l'operatività mediante ripetute simulazioni. Collaborazione e cooperazione devono essere tanto più intense quanto maggiore è il rischio stimato e il numero dei lavoratori, e mirate a garantire assistenza sanitaria tempestiva e di elevato livello qualitativo anche in condizioni estreme.

66**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIALonati D.,
Locatelli C.,
Petroli V.,
Giampreti A.,
Butera R.,
Cocchini T.,
Feniccia L.,
Annibaldi F.,
Manzo L.*In: Clinical and laboratory observations. Atti dell'International Congress of Toxicology ICT XI; Montréal (Canada); 15-19 Luglio 2007 (versione elettronica).***FOOD-BORNE BOTULISM IN ITALY. CLINICAL AND LABORATORY OBSERVATIONS.**

Food-borne botulism (FBo) is a potentially fatal neuroparalytic illness caused by ingestion of food that contains preformed botulinum neurotoxin (BoNT). The vast majority of severe botulism cases involve BoNTs of the types A, B and E. From 1984 through 2005, a total of 267 cases of FBo were identified at the Istituto Superiore di Sanità-NRCB, based on laboratory diagnosis. Eleven cases were fatal. A retrospective analysis of patients referred to Pavia-PCC (year 2005) included 37 ingestions of possibly contaminated food. Diagnosis of suspected FBo was made in 12 patients (age: 9 month-65 years). In 9 cases, the contaminated food was identified. Laboratory assays at NRCB confirmed clinical diagnosis of FBo in six cases. They included 2 cases of type F botulism (reported for the first time in Italy). Seven cases evolved with a typical descending paralysis that required prolonged mechanical ventilation. Nine patients received trivalent antitoxin (anti-BoNT/A, BoNT/B, and BoNT/E). No hypersensitivity reactions were observed. The antidote produced little or no effects on existing neurological deficits. Both the F-type patients received early antitoxin administration but were unresponsive to treatment. Complete recovery occurred in 11 patients over a period from 1 to 8 months. Botulism fatality rates have greatly diminished in the past decades because of advances in intensive care and early laboratory diagnosis. Antitoxin can only neutralize circulating BoNT with no effect on the toxin bound to nerve terminals. The antidote must be given as early as possible to attempt to halt clinical progression.

67**Comunicazione scientifica pubblicata su atti congressuali***Istituto di
PAVIA**Minoia C.,
Sottani C.,
Mantovani A.**In: Convegno Istituto
Superiore di Sanità, 2007.***ASPETTI ANALITICI E METODOLOGICI EMERGENTI NELLA DETERMINAZIONE DI FOLATI NEL SIERO.**

La concentrazione di folati nel siero rappresenta un indicatore biologico importante per valutare lo stato nutrizionale di acido folico nell'uomo. Anche la concentrazione di folati negli eritrociti può rappresentare un utile indicatore, come evidenziato in particolare dagli studi condotti sulla popolazione americana nell'ambito del National Health and Nutrition Examination Survey (NHANES). La metodica analitica più utilizzata per la determinazione di folati nel siero è indubbiamente il Bio-RAD Quantaphase Radioassay. Più recentemente, sono stati pubblicati e proposti metodi che utilizzano la cromatografia liquida ad elevate prestazioni interfacciata a triplo quadrupolo (HPLC-MS-MS, analisi mediante diluizione isotopica) che rispetto al metodo Bio-RAD e al tradizionale metodo microbiologico con *Lactobacillus casei* offrono indiscutibili vantaggi. Innanzitutto la determinazione mediante HPLC-MS-MS permette la separazione e la quantificazione di 5 differenti folati quali l'acido 5-metiltetraidrofolico, l'acido folico, l'acido 5-formiltetraidrofolico, l'acido tetraidrofolico e il 5,10-metilentetraidrofolico. Peraltro è stato dimostrato che il metodo HPLC-MS-MS permette di ottenere ottime correlazioni sia rispetto alla procedura Bio-Rad sia nei confronti del metodo microbiologico. Inoltre, per quanto attiene alla interferenza da antibiotici, è sicuramente più affidabile. Nel merito è opportuno evidenziare che l'analisi secondo la procedura Bio-RAD fornisce basse percentuali di recupero dell'acido 5-metiltetraidrofolico che notoriamente rappresenta la principale forma chimica di folati circolante a livello sierico. Ulteriori vantaggi dell'HPLC-MS-MS sono identificabili nella possibilità di determinare simultaneamente la concentrazione sierica o plasmatica di omocisteina, di acido 5-metiltetraidrofolico e di acido folico, relativamente alla quale si segnala anche la disponibilità del materiale standard di riferimento NIST SRM 1955 Homocysteine and Folate in Frozen Human Serum. Le recenti possibilità analitiche offerte dalla HPLC-MS-MS nella speciazione chimica delle diverse forme ematiche di folati rappresentano quindi un indiscutibile elemento innovativo per indirizzare la supplementazione di acido folico in soggetti a rischio (ad es. durante la gravidanza). A tale scopo la SITOR, Società Italiana di Tossicità della Riproduzione, intende promuovere nel nostro paese studi ad hoc, non trascurando l'attivazione di programmi di qualità interlaboratoriali, a garanzia di una migliore qualità del dato.

68**Comunicazione scientifica pubblicata su atti congressuali***Istituto di
PAVIA**Minoia C.**In: Emissioni autoveicolari
- Qualità dell'Aria
e della Salute; 2007.***EMISSIONI VEICOLARI IN ATMOSFERA URBANA: MARCATORI DI ESPOSIZIONE.**

Nell'esposizione ambientale della popolazione generale a microinquinanti la problematica degli IPA riveste un interesse notevole in quanto è previsto uno specifico obiettivo di qualità per il benzo(a)pirene pari a 1 ng/m³. In realtà l'esposizione a IPA non può essere ricondotta a un'unica sostanza, anche in considerazione che ben sette diversi composti di questa classe sono stati classificati nel Gruppo 2Aa e 2B secondo IARC (possibili e probabili cancerogeni). Trattasi in genere di un'esposizione a miscele complesse la cui composizione può subire variazioni in funzione della loro fonte di origine (area urbana e quindi riferibile alle emissioni veicolari, sorgenti antropiche o industriali). In realtà l'evoluzione dei carburanti per quanto riguarda la loro composizione, la diffusione del convertitore catalitico e la percentuale crescente di autoveicoli alimentati a gasolio introduce variabili che rendono difficoltosa l'individuazione di specifici markers di esposizione a IPA, anche per valutare il peso % in termini contributivi delle varie fonti di origine. Al fine di affrontare in modo razionale e scientifico questo percorso sono stati definiti dei fingerprints per varie sorgenti emmissive di IPA (ad es. caratterizzando le emissioni di differenti insediamenti industriali o di veicoli alimentati con differenti carburanti e in funzione anche della loro vetustà) la cui analisi dettagliata è in grado di fornire informazioni puntuali sui contributi delle diverse fonti emmissive, anche per quanto riguarda le emissioni veicolari. Questo tipo di approccio, opportunamente sviluppato, permetterà ricorrendo a specifici modelli matematici, di verificare, in funzione delle realtà monitorate le possibilità di intervento al fine di assicurare una riduzione delle potenziali fonti inquinanti.

69**Comunicazione scientifica pubblicata su atti congressuali***Istituto di
PAVIA**Minoia C.**In: In P.A.N. Prevenzione,
Alimentazione,
Nutrizione; 2007.***ALIMENTAZIONE, AMBIENTE E CONTAMINANTI: IL CASO DEL KILLER DEGLI SPERMATOZOI.**

Alla via alimentare viene attribuito oggi il contributo prevalente di sostanze organiche persistenti tra i quali figurano anche diversi composti il cui utilizzo è stato vietato da decenni (ci si riferisce ai composti del DDT ma anche all'esaclorobenzene e ai PCB). Numerosi lavori scientifici hanno associato l'esposizione a tali sostanze della popolazione generale con biomarcatori di integrità riproduttiva maschile, che sicuramente rappresenta uno dei settori più esplorati anche in riferimento a composti con caratteristiche di interferenti endocrini. La carenza di studi di dieta totale sull'intake alimentare non permette di verificare in modo accurato le variazioni storiche che sono intervenute, in termini di apporto quantitativo e qualitativo di microinquinanti. In relazione ai possibili effetti che le sopraccitate sostanze possono avere determinato sulla fertilità maschile numerose sono le segnalazioni ad esempio tra esposizione a PCB, p,p'DDE, ftalati e difetti a carico degli spermatozoi. Ad esempio è stato dimostrato che la frazione di spermatozoi Y è più elevata in Svezia e Groenlandia in quanto i soggetti considerati presentavano valori più elevati di PCB. Un'associazione positiva tra percentuale di spermatozoi Y e rapporto PCB/DDE è stata evidenziata sulla popolazione svedese, mentre sulla popolazione polacca l'associazione tra frazione di spermatozoi Y e PCB è risultata negativa.

Un'associazione positiva tra percentuale di spermatozoi con difetti cromatinici (SCSA) e PCB /se maggiori di 51 ng/g) è stato evidenziato nella popolazione europea ma non nella popolazione Inuit. Nello stesso studio nessuna correlazione è emersa con il p,p'-DDE. Un'osservazione critica che si può fare a diversi studi che hanno considerato globalmente una classe di composti (ad es. i PCB) è che la non identificazione dei singoli congeneri può limitare sensibilmente l'affidabilità dello studio e creare fattori di confondimento. Inoltre se è indubbio che l'apporto alimentare di composti organici persistenti (con particolare riferimento agli interferenti endocrini) è andato diminuendo nell'ultimo decennio è pur vero che l'esposizione della popolazione generale ha interessato e interessa un numero più ampio di sostanze, in particolare liposolubili che tendono ad accumularsi nel tessuto adiposo.

70**Comunicazione scientifica pubblicata su atti congressuali***Istituto di
PAVIA**Minoia C.**In: Il^o Giornate Mediche
dell'Ambiente; 2007.***ESPOSIZIONE DELLA POPOLAZIONE INFANTILE A INTERFERENTI ENDOCRINI.**

Nell'esposizione della popolazione infantile a interferenti endocrini la prevalenza degli studi si riferisce all'assunzione alimentare che rappresenta a tutt'oggi la via prevalente di introduzione nell'organismo. Non mancano tuttavia ricerche sull'esposizione inalatoria, in particolare per ftalati e PCB in ambiente indoor. Appare evidente che le conoscenze sviluppate in ambito tossicologico debbano tradursi in azione finalizzate alla regolamentazione e alla valutazione del rischio. Allo stato attuale tale percorso, almeno per quanto riguarda gli interferenti endocrini, presenta numerose lacune anche se appare sempre più evidente un'associazione tra esposizione composti organici persistenti ed effetti sulla salute. Un esempio al riguardo è sicuramente relativo allo sviluppo neurocomportamentale (in particolare durante la gestazione e l'allattamento). È ancora prematuro poter affermare, date le limitate conoscenze anche di tipo epidemiologico se ciò riflette un'azione diretta sul sistema endocrino anche se in alcuni casi è stato dimostrato l'effetto del congenere 153 sulla tiroide. In questo ambito la disponibilità di biomarcatori di esposizione e/o di effetto rappresenta sicuramente un'esigenza sempre più avvertita come hanno dimostrato alcune ricerche sull'esposizione del neonato a ftalati con livelli ematici di gran lunga superiori a quelli della popolazione adulta, a causa di cessioni di queste sostanze da parte di materiali vari utilizzati in ambito ospedaliero e non.

71

Comunicazione scientifica pubblicata su atti congressualiIstituto di
PAVIAMinoia C.,
Bocca B.,
Ronchi A.,
Forte G.,
Pino A.,
Finozzi E.,
Catenacci G.,
Conti M.E.,
Alimonti A.*In: Atti del 7th International
Symposium on Biological
Monitoring; 2007; 50.***REFERENCE VALUES OF 47 TRACE ELEMENTS IN WHOLE BLOOD, SERUM AND URINE BY DRC-ICP-MS AND SF-ICP-MS IN TWO ITALIAN POPULATION GROUPS FROM LOMBARDIA AND LAZIO REGIONS.**

The availability of Reference values (RVS) for Trace Elements (TEs) in biological fluids for general population deserves special attention both at environmental and occupational levels. Moreover, thanks to the multi-elemental capability of instrumental techniques as ICP-MS, the analytical and toxicological information has become sensibly wider than past. In the production of the actual RBVs major difficulties arise from $f^{\circ}g/L$, the very low concentration of the TEs, at levels of ng/L.

Therefore, the development and validation of methods, also including the calculation of measurements uncertainty able to reveal TEs at their concentrations in matrices is mandatory. Data on two groups of the Italian population were reported in this study; one composed of 160 individuals living in Lombardia Region, age ranged from 18 to 87 years (mean 48,6 years); the other living in Lazio Regions (120 subjects, 20-61 years aged, mean aged 42,0 years). The a priori selection of subjects was used, by an informative questionnaire for the collection of data on life styles, dietary habits, physiological variables, etc. Quantifications were carried out on the whole blood, serum/plasma and urine. Special care was posed on the control of pre-analytical factors occurring in the sample collection, storage and treatment steps. Elements were quantified by Dinamic Cell Reaction and Sector Field-ICP-MS, this last operating at medium and high resolution in order to assure for each element an efficient separation from the relevant polyatomic interferences. As an example, data on measurement uncertainty obtained for some TE with both techniques was also given to confirm the good agreement between the two percentiles, and data of $g\ g^{-1}$ of creatinine. The found VRs were reported and compared with those recently reported in literature so as to show the potential differences with other European and non-European populations groups. In conclusion, the effectiveness of the term RV for essential and non essential TE wa also commented. Terms as Background value, Baseline Concentration, Reference Value of Consensus and Tentative Reference Value were discussed.

72

Comunicazione scientifica pubblicata su atti congressualiIstituto di
PAVIAMinoia C.,
Sottani C.*In: Convegno Istituto
Superiore di Sanità, 2007.***LA VALUTAZIONE DEL RISCHIO NELL'ESPOSIZIONE A CHEMIOTERAPICI ANTIBLASTICI.**

Sono state presentate e descritte le strategie di monitoraggio ambientale e biologico per quanto attiene alla valutazione dell'esposizione di personale sanitario (preparatori e somministratori di farmaci antineoplastici). Trattandosi di un'esposizione multipla a livello di microdosi di un elevato numero di principi attivi (sino a 40 differenti farmaci in alcune strutture ospedaliere) una delle problematiche è la definizione del profilo di analiti da utilizzare come markers, tenendo presente che un elevato numero di chemioterapici antiblastici è stato classificato da IARC nel gruppo 1, 2A, 2B e 3. A tale scopo, avvalendosi di tecniche strumentali come l'HPLC-MS-MS in questi ultimi anni si è cercato di sviluppare e valicare metodi analitici che permettessero la determinazione contemporanea di più principi attivi sulla stessa matrice (wipe-tests, pads come matrici ambientali e urina come matrice biologica). Un'ulteriore aspetto sul quale si è insistito è la validazione del metodo per l'incertezza estesa per cui accanto alla possibilità di dosare 5-6 differenti principi attivi viene fornito per ciascuno di essi anche il dato di incertezza estesa ai valori caratteristici di esposizione. Una particolare attenzione è stata dedicata alla sensibilità analitica dei metodi utilizzati in merito ai quali la DRC-ICP-MS si è rivelata una scelta strumentale determinante nella determinazione di platino per valutare l'assorbimento da cloroplatinati (cis-Pt, Carbo-Pt, oxali-Pt). Nel merito il metodo per il Pt in urina ha fornito un LOD di 0,5 ng/l con la possibilità di determinare i valori di riferimento di questo indicatore biologico nella popolazione generale (è stato rilevato un valore medio prossimo a 4 ng/L). Ciò ha permesso di identificare un'importante variabile di confondimento (portatori di protesi odontoiatriche in oro) in grado di elevare sensibilmente l'escrezione urinaria di Pt.

73**Comunicazione scientifica pubblicata su atti congressuali**

Istituto di
PAVIA

Minoia C.,
Santamaria R.,
Turci R.,
Mantovani A.

In: *Fattori Ambientali
e Salute Riproduttiva*;
2007.

I VALORI DI RIFERIMENTO DEI BIOMARCATORI DI ESPOSIZIONE COME START POINT DELLE ATTIVITÀ DI PREVENZIONE: L'ESEMPIO DEI COMPOSTI ORGANOALOGENATI PERSISTENTI.

La produzione di sostanze chimiche e la loro immissione in ambiente ha prodotto inevitabili influenze sulla catena alimentare umana. Al riguardo una classe di composti che ha assunto rilevanza è senza dubbio quella dei Composti Organici Persistenti, tra i quali figurano diverse sostanze con caratteristiche di interferenti endocrini. La persistenza nell'organismo umano è facilitata dalla liposolubilità di questi composti che si accumulano quindi nel tessuto adiposo con un'emivita dell'ordine di diverse decine di anni, ovviamente in funzione della biopersistenza del tipo di composti desiderati. L'accumulo storico, caratterizzato negli ultimi decenni anche da decrementi apprezzabili a livello ematico di composti organoclorurati persistenti (Esaclorobenzene, PCB, DDT ecc) ha di fatto determinato una condizione di esposizione multipla a un numero molto elevato di sostanze chimiche, per quali si ignorano eventuali effetti sinergici o comunque affetti alla salute. È stato quindi condotto uno studio per la determinazione di 31 differenti composti organoclorurati in una casistica di 95 soggetti residenti a Pavia e a Novafeltria (Pesaro) che ha evidenziato come diversi composti, oggi non più utilizzati perché vietati, siano ancora presenti. Ci si riferisce ad esempio a 5 diverse forme chimiche del DDT dove l'o,p'-DDT è stato rilevato ad esempio nell'83% della casistica considerata a una concentrazione media di 197 ng/g di lipidi, un valore superiore a quello del congenere 153 (il composti più abbondante dei PCB rilevabili nel siero) che presentava un valore medio di 131 mg/g lipidi, con una positività in termini di frequenza del 99%. Da rilevare tra l'altro la presenza dell'esaclorobenzene (100% di frequenza a una concentrazione media di 54 ng/mg lipidi) e del p,p'-DDE (valore medio di 115 ng g lipidi) con un riscontro del 98% nei gruppi di popolazione esaminata.

74**Comunicazione scientifica pubblicata su atti congressuali**

Istituto di
PAVIA

Minoia C.,
Santamaria R.,
Turci R.,
Mantovani A.

In: *Fattori Ambientali
e Salute Riproduttiva*;
2007.

INFERTILITÀ ED ESPOSIZIONE AMBIENTALE A COMPOSTI INTERFERENTI ENDOCRINI: SUGGERIMENTI, IPOTESI E/O EVIDENZE SCIENTIFICHE?

Tra i composti più studiati risultano indubbiamente i PCB, gli ftalati, i metaboliti del DDT, quali interferenti e anche alcuni antiparassitari (ad es. chlorpyrifos). Per i composti liposolubili un aspetto che è stato indagato è il trasferimento transgenerazionale di questi composti. Ciò ha orientato alcune ricerche a indagare i livelli ematici (sierici) della madre di figli maschi infertili. Uno studio al riguardo ha riscontrato che il p-p'-DDE livelli più elevati nelle madri di soggetti dispermici. Occorre rilevare che in termini di differenze con gruppi di controllo le differenze osservate nei valori dei biomarcatori di esposizione mostrano differenze scarsamente significative o comunque al limite della significatività statistica. Un dubbio che talvolta permane è che esse siano compatibili con l'incertezza delle metodiche analitiche utilizzate, non sempre adeguate a questo tipo di studio. Anche considerato casistiche di infertili dispermici con infertili normospermici sono emerse differenze disgnificative del p,p'-DDE ma anche dei PCB. Un aspetto comunque alla prevalenza degli studi è che emergono orientamenti sull'azione di composti organici persistenti liposolubili ma dal punto di vista quantitativo le variazioni osservate nelle concentrazioni degli analiti a livello ematico sono in genere piuttosto contenute. In realtà potrebbe essere auspicabile, per futuri studi correlare l'infertilità maschile e le alterazioni rilevate (numero di spermatozoi, motilità, anomalie morfologiche, difetti cromatinici) avendo a disposizione uno spettro piuttosto ampio di informazioni analitiche in quanto la loro origine potrebbe derivare da meccanismi sinergici tra i diversi xenobiotici. Allo stesso tempo è necessario quando fare ricorso, come è il caso degli ftalati, a una determinazione estesa ai principali metaboliti urinari, fermo restando l'importanza di disporre di valori di riferimento e soprattutto previa identificazione delle variabili fisiologiche, alimentari e/o voluttuarie maggiormente significative.

75

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Moramarco L.P.,
Poggi G.,
Massa Saluzzo C.,
Azzaretti A.,
Rodolico G.,
Teragni C.,
Minoia C.,
Di Maria F.,
Quaretti P.

In: *Convegno Nazionale della Sezione di Radiologica Vascolare ed Interventistica della S.I.R.M.*; Pisa, 2007; 139-140.

TACE CON HEPASPHERE PRECARICATE CON OXALIPLATINO NEI TUMORI EPATICI NON RESECABILI: FATTIBILITÀ E VALUTAZIONE FARMACOCINETICA IN VIVO. STUDIO PILOTA.

Lo studio pre-clinico in vitro è stato condotto utilizzando uno spettrometro di massa accoppiato a plasma con tecnica a induzione (ICP-MS) per quantificare la capacità delle microsferi di legare oxaliplatino come platino inorganico a differenti intervalli di tempo. Le microsferi sono state diluite in mezzo di contrasto (Visipaque 270). La soluzione ottenuta è stata microfiltrata, diluita e successivamente analizzata. A ogni intervallo di tempo prefissato, il livello di platino libero è risultato inferiore al limite di rivelabilità, il che suggerisce un legame completo tra microsferi e oxaliplatino. Il fattore di espansione delle microsferi dopo caricamento con oxaliplatino e Visipaque è stato di 4:1. Sono quindi stati trattati 12 pazienti con 29 sessioni di TACE (da 1 a 4 per paziente) e 10 sessioni di RTFA come terapia aggiuntiva in 8 pazienti (da 0 a 2 per paziente). L'età media era di 63,8 anni, range 51-83 anni. Cinque pazienti presentavano un colangiocarcinoma e 7 presentavano metastasi epatiche da carcinoma coloretale. Ognuno dei pazienti aveva intrapreso regimi chemioterapici sistemici in precedenza (4 pazienti più di una volta). Tutti presentavano almeno una lesione epatica non resecabile; 5 pazienti presentavano 3 o più lesioni. Non si sono verificati decessi o complicanze maggiori alla procedura. La concentrazione media di oxaliplatino all'interno della lesione neoplastica si è rivelata 20 volte superiore alla concentrazione perilesionale. Il picco di concentrazione plasmatica (media 526,7 ug/L) è stato raggiunto a circa 4 ore dalla TACE, con un ritorno al valore basale dopo 72 ore. Non si sono verificate complicanze maggiori dopo il trattamento. Il controllo TC e PET ha dimostrato risposta obiettiva al trattamento in 6 pazienti. La conclusione del presente studio è che la TACE con microsferi precaricate con oxaliplatino seguita da RTFA è un trattamento sicuro e fattibile con complicanze maggiori e con un profilo farmacocinetico favorevole.

76

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Petrolini V.,
Locatelli C.,
Giampreti A.,
Lonati D.,
Butera R.,
Manzo L.

In: *Atti del XXVII International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT)*; 2007; 45; 361.

FATAL CASE OF SODIUM CHLORATE SELF POISONING.

Objective: Chlorate salts (Ch-s) poisoning is associated with high mortality rate (1) and requires prompt supportive and antidotal treatment: the role of invasive depuration procedures is not established. The main mechanism of toxicity of Ch-s is related to the strong oxidative action on all cells and tissues, mainly on erythrocyte cell membrane and haemoglobin: this causes massive haemolysis and methaemoglobinemia (metHb) (2) followed by disseminated intravascular coagulation and acute renal failure. We describe a case in which all the available treatments were ineffective.

Case Report: A 28-year-old man was admitted to the emergency department (ED) 1.5 hours after voluntary ingestion of unknown amount of the Radical® herbicide (sodium chlorate 38%). At admission, the patient showed only diarrhoea, without other symptoms or cyanosis: the first laboratory investigations and blood gas-analysis were normal. An extensive gastric lavage was immediately performed, followed by activated charcoal and magnesium sulphate administration. Sub-cyanosis (labial, unguis) and then massive cyanosis with metHb 54.4%, trismus and respiratory arrest (requiring mechanical ventilation) progressively appeared in 90 minutes. Three hours later the clinical course was characterized by hypotension (requiring fluids and sympathomimetics), rhabdomyolysis, massive haemolysis, renal failure, metabolic acidosis, coagulation disorders and cardiac tissue hypoxia: metHb reached 81%. Intravenous high dose sodium bicarbonate was administered to treat both metabolic acidosis and rhabdomyolysis. Antidotal treatment with methylene blue (2.5 mg/kg) and Na-thiosulfate (5 g), associated with 3 exchange-transfusion sessions combined with continuous haemodialysis, fresh frozen plasma and blood transfusion were applied. Despite this, the patient died 20 hours after admission.

Conclusions: Ch-s poisoning is a potentially fatal event in which diarrhoea can be the only symptom on presentation. Cyanosis and metHb are the specific signs of poisoning, but chlorate chromatographic analysis is unavailable in EDs (3). Massive haemolysis, coagulation dysfunction, renal failure and cardiovascular collapse complicated the clinical course. Methyleneblue can reduce metHb to haemoglobin in the first phase, but this efficacy can be limited by Ch-s effect of inactivation of glucose-6-phosphate-dehydrogenase (4), or by the presence of haemolysis; Na-thiosulfate may inactivate the chlorate-ion, but its use is controversial.

References: 1. Helliwell M, Nunn J. Mortality in sodium chlorate poisoning. *Br Med J* 1979; 1: 1119.
2. Steffen C, Wetzel E. Chlorate poisoning: mechanism of toxicity. *Toxicology* 1993; 84: 217-231.
3. Eysseric H, Vincent F, Peoc'h M, et al. A fatal case of chlorate poisoning: confirmation by ion-chromatography of body fluids. *J Forensic Sci* 2000; 45: 474-477.
4. Singelmann E, Wetzel E, Adler G, et al. Erythrocyte membrane alterations as the basis of chlorate toxicity. *Toxicology* 1984; 30: 135-147.

77**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIAPetrolini V.,
Locatelli C.,
Mela L.,
Lonati D.,
Calvi G.,
Manzo L.*In: Atti del 5° Congresso Nazionale della Società Italiana di Anestesia, Rianimazione, Emergenza e Dolore (SIARED); Napoli, 20-22 Settembre 2007; 147-153.***GLI ANTIDOTI: DISPONIBILITÀ NEL SISTEMA SANITARIO E GESTIONE DELLA SCORTA NAZIONALE PER LE EMERGENZE CHIMICHE MAGGIORI.**

La realizzazione della Banca dati nazionale degli antidoti è in linea con gli obiettivi del Ministero della Salute relativi al miglioramento della reperibilità di antidoti sul territorio nazionale, e contribuisce a facilitarne la disponibilità come indicato da documenti formali dell'Unione Europea e da raccomandazioni di agenzie soprannazionali quali l'International Programme on Chemical Safety (IPCS) dell'OMS. La disponibilità di queste informazioni in rete può inoltre (a) contribuire a migliorare la corretta acquisizione e stoccaggio di antidoti presso ogni servizio secondo criteri che tengano conto della disponibilità già presente sul territorio, delle caratteristiche operative delle singole strutture e delle peculiarità geografiche locali, (b) consentire un utilizzo più appropriato delle risorse senza cadere nell'errata e colpevole carenza di farmaci che, per quanto di raro impiego, sono salvavita, e (c) contribuire a migliorare l'appropriatezza delle cure fornite attraverso la corretta disponibilità di antidoti. La disponibilità di antidoti nell'industria a rischio rilevante consente di disporre in situ per il primo soccorso e successivamente anche nell'ospedale di riferimento degli antidoti necessari per il trattamento di intossicazioni rare per le quali non c'è disponibilità dell'antidoto ne SSN. Questo è in linea con quanto previsto dalla Risoluzione del Consiglio e dei Rappresentati dei Governi degli Stati Membri relativa al miglioramento della prevenzione e del trattamento delle intossicazioni acute nell'uomo (Risoluzione CEE 90/C 329/03), nonché dalle normative italiane per la sicurezza sui luoghi di lavoro (DLvo 626/94 e successive modifiche e integrazioni) e per il controllo dei pericoli da incidenti rilevanti (Legge 334/99 e successive modifiche e integrazioni). L'acquisizione e la disponibilità di antidoti della Scorta Nazionale Strategica, istituita dal DPC e ora gestita dal Ministero della Salute, ha consentito di disporre oggi dei mezzi necessari per far fronte a trattamenti antidotici in caso di incidenti di massa. Il valore aggiuntivo di questo sistema è che, benché creato sull'onda della minaccia del terrorismo, esso dovrebbe rimanere operativo nel futuro anche per gli incidenti chimici rilevanti di natura non terroristica. Questo modello, integrato con le competenze idonee e con altre risorse necessarie (mezzi di decontaminazione, farmaci sintomatici, laboratori) aumenta le capacità del sistema Paese di affrontare questi eventi critici. L'utilità dei mezzi resi disponibili dai modelli descritti è subordinata al loro corretto utilizzo: ciò richiede un inquadramento specialistico da parte di un Centro Antiveneni in grado di porre una diagnosi e un'indicazione corretta alla somministrazione dell'antidoto.

78**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIAPetrolini V.,
Lonati D.,
Giampreti A.,
Locatelli C.,
Butera R.,
Manzo L.*In: Atti del 4th Mediterranean Emergency Medicine Congress (MEMC); Sorrento, 15-19 Settembre 2007 (versione elettronica).***A SEVERE CASE OF ACCIDENTAL PARAQUAT POISONING.**

Paraquat (P) poisoning is a potentially serious event that could require, in absence of a specific antidotic treatment, the use of invasive procedures and aggressive pharmacological therapies. Among 218 cases of exposure to pesticides referred to Pavia-Poison-Centre over a 5 month period, 5 (2.3%) were of P exposure. Among these, 2 were of fatal voluntary ingestion and 2 of accidental non toxic exposure: we describe the fifth case in which all the available treatments were applied. A 46 year-old man affected by chronic obstructive bronchopneumopathy (COPD) was admitted to emergency room 1.5 hour after accidental ingestion of about 80 ml of a 11.7% P and 5.9% diquat solution. At admission the patient was asymptomatic. Gastric lavage, activated-charcoal and cathartics were immediately practised. Fuller's-earth solution every 2 hours for one day, forced diuresis, Nacetylcysteine, and vitamin C were promptly administered. P blood level at 8 hours after ingestion was 1.9 mg/L, so three charcoal hemoperfusion (HPC) sessions were applied. At the end of HPC, a pulsed-cyclophosphamide-methylprednisolone-therapy was started. Vitamin E was started by day 4. P blood levels at day 4 and 8 resulted undetectable. Pulmonary function tests, gas analysis, and chest radiographs during hospitalization were compatible with patient's disease (COPD). The patient remained always asymptomatic and was discharged at day 15 with dexamethasone 30 mg/day for 45 days, followed by 12 mg/day for 3 months. At follow-up, pulmonary and liver function tests, gas analysis (repeated one time a week up to 3 months after discharging) and repeated chest radiographs resulted without abnormalities: at 8 months the patient's follow-up was stopped. P poisoning is often associated with a dramatic clinical course. HPC can reduce P plasma level and NAC, antioxidants and corticosteroids, especially combined with cyclophosphamide may offer some benefits by preventing oxidative damage and pulmonary fibrosis. In this case, the mortality rate related with patient's plasma level was about 80-90%; early diagnosis, decontamination and subsequent treatment may have played a discriminant role for the successful management.

79

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Petrolini V.,
Lonati D.,
Rocchi L.,
Baldi M.,
Campaila M.,
Guido S.

In: Atti del
4th Mediterranean
Emergency Medicine
Congress (MEMC);
Sorrento,
15-19 Settembre 2007
(versione elettronica).

ACUTE NEUROTOXICITY AFTER YOHIMBINE CONSUMPTION IN A BODY-BUILDER.

Background: Yohimbine (Yo) is an alkaloid obtained from *Corynanthe Yohimbe* and other biological sources. Yo is clinically applied in the treatment of certain types of erectile impotence. Yo has undergone a resurgence in street use as an aphrodisiac and mild hallucinogen; in recent years Yo is very diffusely used in the body-building community for its hypothesized lipolytic and sympathicomimetic effects. We describe a case in which severe acute neurotoxic effects developed after documented Yo oral ingestion in a bodybuilder.

Case: A 37 year-old man after ingestion of an estimated 5 grams of Yo and niacin for a body-building competition presented with a clinical picture characterized by early generalized malaise, vomiting, loss of consciousness and seizures that spontaneously resolved after two minutes. At first evaluation the patient presented with a GCS 3, and orotracheal intubation and fluids infusion were immediately practised. At admission to the ICU the patient presented: hypertension (acme 259/107 mmHg), tachycardia (acme 140 pulse/minutes) and was treated with furosemide and labetalol; chest radiographs and brain CT were normal. The patient's history was negative for neurological diseases. An extensive gastric lavage was immediately performed, followed by oral administration of activated charcoal and cathartics. After 12 hours the patient was extubated with normal hemodynamic parameters and neurological examination. The Yo blood levels at about 3, 6, 14 and 22 hours after ingestion were 5240 ng/ml, 2250 ng/ml, 1530 ng/ml, 865 ng/ml respectively.

Discussion: Yo utilization in the body-building community is a known problem but few data are available about its toxicity and related toxic blood levels. The most common adverse effects from Yo administration include antidiuresis, tachycardia, hypertension, vasodilation, nausea, tremor, irritability, dizziness, headache and hallucinations. In this case report severe hemodynamic, and neurological manifestations are described and a possible correlation with very high levels of Yo blood concentration, in the patient could be evidenced.

80

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Petrolini V.,
Morabito N.,
Maggio C.,
Sartori F.,
Locatelli C.,
Manzo L.

In: Atti del
4th Mediterranean
Emergency Medicine
Congress (MEMC);
Sorrento,
15-19 Settembre 2007
(versione elettronica).

UTILITÀ DI STRUMENTI SEMPLICI DI TELEMEDICINA PER LA GESTIONE DI INTOSSICAZIONI IN SITUAZIONI DIFFICILI.

La corretta gestione di un'intossicazione acuta da piante non può prescindere dal riconoscimento del vegetale e dalla conoscenza della sua tossicità. Ciò può richiedere l'integrazione di più competenze professionali raramente disponibili contemporaneamente nella stessa sede, specie se il luogo di cura del paziente è particolarmente isolato. L'uso di tecniche semplici di telemedicina può contribuire a migliorare la gestione dei casi.

Caso Clinico: Nel tardo pomeriggio, il medico di Pronto Soccorso dell'isola Lampedusa (PS) richiede consulenza specialistica al Centro Antiveneni di Pavia (CAV): una bimba di 8 anni, poco attendibile per ritardo mentale, ha masticato e forse ingerito un vegetale. Il riconoscimento botanico non è effettuabile in sede. Sono presenti ustioni della lingua, ma non sintomi sistemici. Vengono perciò trasmesse al CAV immagini digitali della paziente e della pianta; un esperto botanico a cui vengono rinviate queste ultime riconosce la pianta come appartenente alla famiglia delle Crassulacee. Alla luce del quadro clinico e della tossicità del vegetale (potenziale tossicità locale ma non sistemica) i medici di CAV e PS valutano il caso gestibile con le risorse locali e quindi non necessario il trasferimento in urgenza (elicottero) verso un presidio ospedaliero siciliano. Viene impostato un trattamento sintomatico e un monitoraggio della calcemia: la paziente viene dimessa dal PS il giorno dopo in buono stato di salute.

Discussione: L'attività dei CAV è un esempio tra i più vecchi e semplici di telemedicina, attraverso il quale i medici fruiscono real time di una consulenza esperta da sede remota. Aggiungere la trasmissione di immagini consente di migliorare la valutazione clinica del paziente da parte dello specialista e, tramite il coinvolgimento delle competenze adeguate, di riconoscere gli agenti assunti. A ciò consegue una più corretta gestione clinica e l'ottimizzazione delle risorse disponibili, soprattutto quando il medico urgentista opera in sedi isolate. Il riconoscimento di una pianta a tossicità sistemica avrebbe indicato percorsi diagnostico terapeutici più impegnativi e costosi.

81**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIAPetrolini V.,
Locatelli C.,
Lonati D.,
Giampreti A.,
Butera R.,
Manzo L.*In: Atti del 1^{er} Congrès
de la Société Française
de Médecine d'Urgence;
Parigi (Francia),
30 Maggio - 1 Giugno 2007;
Journal Européen
des Urgences (JEUR)
2007; 20; 1: S166.***GRAVITÉ ET ÉVOLUTION CLINIQUE DE 80 CAS DE MORSURE DE VIPÈRE EN ITALIE.**

La morsure de vipère est une intoxication caractérisée d'une gravité potentielle qui exige une immédiate évacuation médicale aux services d'urgence hospitaliers. Aussi, les patients avec un bas index de gravité à la prise en charge peuvent avoir un nombre négligeable de chance de s'aggraver pendant le premières 12 heures qui suivent la morsure: pourtant une observation d'au moins 12 heures est recommandable pour une correcte gestion médicale dans tous les cas de morsure de vipère.

82**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIAPignataro A.,
Lanza V.,
Passafiume M.,
Calderone L.,
Locatelli C.*In: Atti del XXVII
International Congress
of the European
Association of Poisons
Centres and Clinical
Toxicologists (EAPCCT);
Atene (Grecia),
1-4 Maggio 2007;
45; 341.***ANTIVENOM FOR VIPER SNAKEBITE: WHEN AND HOW MUCH - A CASE REPORT.**

Objective: The use of snake-antivenoms is limited in Italy by their shortage on the market and the restricted hospital use. In case of uncertain snake-bite or when the victim is admitted to the emergency department (ED) many hours after the bite, the dose of antivenom that needs to be administered is controversial.

Case Report: A 68-year-old man was admitted to ED two hours after a bite by an unidentified animal in the finger while he was picking up vegetables. The man complained of a small sting and there were no local or general signs on first examination: he was discharged from hospital without treatment. Twelve hours later, the man was readmitted to ED showing a large oedema on the bitten arm, and complaining of severe pain and paresthesia. Vital signs were normal and laboratory analysis revealed only D-Dimer alterations (12.94 mcg/ml). After a consultation with the Poison Centre, the administration of nadroparin calcium (5700 U.I. subcutaneously) and European Viper Venom Antiserum (Fab-antivenom, 1 vial in normal saline solution, intravenously) were started; the patient was admitted to the intensive care unit (ICU) for further monitoring and treatment. In ICU the patient was submitted to hourly checks of the circumference of hand, forearm, thorax and neck of the affected body side. During the first six hours the patient's vital signs remained stable and there was a slight reduction of angioedema and pain of the arm. A subsequent increase in local swelling and angioedema forced the second dose of Fab-antivenom, with consequent stabilization of the lesions. Next morning, the hemithorax and the neck of the same side became oedematous and the patient required oxygen by face-mask to maintain a normal saturation rate and a third dose of Fab-antivenom with stopping of progression of the oedema. An echo-doppler exam of the bitten arm revealed no obstruction of arterial and venous vasculature. The D-Dimer value returned to normal in two days and, on the third day, the patient was transferred to a medical ward.

Conclusion: The report of severe anaphylactic reactions to viper antivenom and the shortage on the Italian market has restricted its indications to severe cases. In this case, a late diagnosis required several doses at different times of antivenom. When the animal is unknown, clinical and laboratory monitoring is essential to precise timing and dosing of antivenom.

83**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIAPodio S.,
Petrolini V.,
Lonati D.,
Cerruti A.,
Pesenti Campagnoni M.In: Atti del
4th Mediterranean
Emergency Medicine
Congress (MEMC);
Sorrento,
15-19 Settembre 2007
(versione elettronica).**UN SINGOLARE CASO DI TOSSICITÀ DA PRODOTTO “NON TOSSICO”.**

L'emulsione acquosa di silani/silossani (Pulvistop Geal®), usata in edilizia è stata finora considerata non pericolosa per la salute. Descriviamo un caso di alveolite chimica da emulsione acquosa di silani/silossani. Un giovane di 34 anni, di normale costituzione fisica ed in buona salute, giungeva in PS lamentando dolore puntorio toracico insorto dopo l'applicazione di emulsione di silani/silossani mediante nebulizzazione da compressore protratta per circa 2 ore in ambiente chiuso, aggravatosi nelle ore successive con dispnea antalgica. All'arrivo in PS, 8 ore dopo l'esposizione, frequenza respiratoria ed EO dell'apparato polmonare erano normali. Veniva informato il Centro Antiveneni (CAV) di Pavia che, in base alla scheda tecnica del prodotto, riferiva limitata tossicità della sostanza. Viste l'entità del dolore, la SatO₂ di 92% in aria ambiente e la rilevante ipossia arteriosa (49,8 mmHg), d'intesa con i consulenti del CAV, veniva sottoposto ad Rx torace (normale) e, successivamente, a TC del torace con evidenza nei campi superiori di imbibizione edematosa alveolo-interstiziale bilateralmente. Il paziente veniva quindi sottoposto a terapia con CPAP, cortisonici ed antibiotici con rapido miglioramento delle condizioni generali e polmonari con completa restituito ad integrum nei 3 giorni successivi. Sulla base di questi dati il CAV di Pavia ha provveduto ad informare la ditta produttrice ottenendo sia l'aggiunta della frase di rischio S23 (non respirare vapori/aerosol) nella scheda tecnica e sia la modifica relativa alla modalità di utilizzo (che comprende il divieto di utilizzo del prodotto con compressori) che è stata inserita anche nell'etichetta. Il caso riportato conferma che le modalità di impiego del prodotto possono avere rilevanza sulle conseguenze tossicologiche dello stesso e quanto sia importante una raccolta anamnestica mirata. Evidenzia inoltre l'opportunità di mantenere un elevato indice di sospetto anche in presenza di dichiarata “non tossicità” del prodotto.

84**Comunicazione scientifica pubblicata su atti congressuali**Istituto di
PAVIAPoggi G.,
Quaretti P.,
Minoia C.,
Massa Saluzzi C.,
Riccardi A.,
Gaggeri E.,
Teragni C.,
Del Monte A.,
Amatu A.,
Ronchi A.,
Sottani C.,
Saini G.,
Bernieri S.,
Bernardo G.In: World Conference
of Interventional
Oncology, Washington,
DC, USA; 2007.**TRANSARTERIAL HEPATIC CHEMOEMBOLIZATION (TACE) WITH OXALIPLATIN-LOADED MICROSPHERES (HEPASPHERE) AND PERCUTANEOUS RADIOFREQUENCY THERMAL ABLATION (RFA) AS A COMBINED THERAPY FOR UNRESECTABLE HEPATIC TUMOURS.**

The use of locoregional therapies (TACE and RFA) is increasing in the management of hepatic tumours. Preliminary study of TACE with microspheres have shown advantages in comparison with lipiodol. Such particles, besides selective embolization of feeding arteries allow carrying and releasing drugs directly into the lesions. RFTA has showed a synergistic effect when combined with TACE: The aim of this study was to evaluate the in vitro capability of Hepasphere (Biosphere Medical) to bind oxaliplatin, the feasibility of TACE with oxaliplatin-loaded microspheres followed by RFTA in patients with unresectable hepatic tumours and to determine their in vivo pharmacokinetic profile. Pre-clinical a study in vitro was done using Inductively Coupled Plasma Mass spectrometer (ICP-MS) to quantify oxaliplatin binding microspheres as inorganic platinum at different time points. Oxaliplatin was evaluated by ICP-MS in plasma, urine, ultrafiltrate and liver biopsies, as inorganic platinum. Liver biopsies were pre-treated in nitric acid at 65% and the diluted (1:40 v/v), before tissue platinum analysis by ICP-MS. We treated twelve patients with 29 sessions of TACE (from 1 to 4 patient) and 10 sessions of percutaneous RFA (from 0-2 per patient). The mean age was 63.8 years (range 51-83). Five patients had cholangiocarcinoma and seven had colorectal metastases. All patients received previously chemotherapeutic regimens (four patients more than one). All patients have at least one unresectable hepatic lesions; five patients had three or more hepatic lesions. The mean oxaliplatin concentration within the tumor was twenty-times higher than peri-lesion concentration (range 1.2-71.2 ug/g). The peak in plasma concentration (mean 526 ug/L) occurred at approximately 4 hours without return to baseline after 72 hours. No major adverse effect (AE G3/4) occurred after treatment. CT and PET showed objective responses in six patients. TACE with microspheres followed by RFTA is a safe and feasible treatment without major adverse events and with a favourable pharmacokinetic profile.

85**Comunicazione scientifica pubblicata su atti congressuali***Istituto di
PAVIA**Tiboni G.M.,
Turci R.,
Giampietro F.,
Palumbo P.,
Minoia C.**In: Atti del Convegno:
Fattori Ambientali
e Salute Riproduttiva;
Pescara, 8-9 Giugno 2007.***LIVELLI DI BIFENILI POLICLORURATI (PCB) NEL FLUIDO FOLLICOLARE DI PAZIENTI SOTTOPOSTE A TECNICHE DI PROCREAZIONE ASSISTITA.**

In Italia 1 coppia su 5 presenta problemi di fertilità. Si stima che siano circa 60.000 le coppie che ogni anno in Italia presentano problemi di fertilità.

Questi problemi possono essere ricondotti all'esposizione a sostanze chimiche, tra cui i PCB. Essi appartengono alla categoria dei persistent organochlorinated pollutants (POPs) ed esistono 209 congeneri con differenti effetti biologici. I PCB sono caratterizzati da lunga biopersistenza nell'ambiente, diffusione ambientale e bassa solubilità in acqua ed elevata liposolubilità che favorisce il bioaccumulo nei tessuti grassi. Tra i possibili effetti tossici da PCB, sono noti i seguenti: Epatotossicità, alterazioni della funzione tiroidea, immunotossicità, alterazione dello sviluppo neuropsicologico, cancerogenesi, artrite reumatoide, e tossicità riproduttiva. Obiettivo del presente studio è valutare i livelli di contaminazione sierica e follicolare da PCB in una popolazione di donne italiane sottoposte a tecniche di procreazione assistita. Inoltre, si intende verificare il possibile impatto dell'esposizione a PCB sull'esito delle tecniche di procreazione assistita.

I PCB sono risultati dosabili nel siero di tutte le pazienti, e nel fluido follicolare del 50% delle pazienti.

Inoltre:

- le concentrazioni follicolari erano circa 1/3 delle concentrazioni sieriche;
- si è osservato un aumento significativo delle concentrazioni sieriche e follicolari con l'aumento dell'età della paziente;
- si è osservata una tendenza alla diminuzione delle concentrazioni sieriche e follicolari con l'aumento dell'indice di massa corporea;
- non sono stati rilevati apparenti effetti negativi sull'esito delle tecniche di procreazione assistita.

86**Comunicazione scientifica pubblicata su atti congressuali***Istituto di
PAVIA**Turci R.**In: Atti del 10th GERPAC
Conference and
5th European Congress,
1st BOPP, Mol; Belgium,
2007.***MONITORING OCCUPATIONAL EXPOSURE TO ANTINEOPLASTIC DRUGS IN SEVEN ITALIAN HOSPITALS: THE EFFECT OF ADHERENCE TO GUIDELINES.**

Healthcare personnel handling cytostatic antineoplastic agents may be exposed to these drugs.

In seven hospitals located in Central Italy, periodic assessments were scheduled to verify continuing compliance with guidelines over a four-years period.

A detailed questionnaire was completed by the personnel working in each department to collect important information about their occupational history, work practices, use of protective measures, etc.

As regards biological monitoring, urine samples were collected at the beginning and at the end shift

All the samples were found to be below the limit of quantitation.

As regards environmental monitoring, adherence to guidelines has resulted in very low-level exposure

In general, contamination was mainly found on pumps and i.v. tubing in the preparation area

In some departments, low levels were detected on the floors and on the working trays inside the BSC as well as outside the preparation area.

No air samples was found to be positive. This confirmed the effectiveness of the BSCs.

These results confirm that a cost-effective monitoring regime, including:

- fast and simple sample pre-treatment procedure;
- simultaneous determination of the analytes and their metabolites; (e.g. four anthracyclines, gemcitabine + 2,2'-dFdU);
- validated procedure and uncertainty evaluation;
- periodic surveys;

is the adequate approach for the collection of reliable exposure data and thus for effective intervention.

87

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Turci R.,
Gaiardi S.,
Mazzotti M.,
Coghi R.,
Del Bianco M.,
Pari P.,
Gabellini M.,
Patone M.,
Zignani M.,
Ghetti M.,
Castrìotta C.,
Severi P.,
Sottani C.,
Minoia C.

In: *Atti del 7th International Symposium on Biological Monitoring; 2007; 63.*

OCCUPATIONAL EXPOSURE TO ANTINEOPLASTIC DRUGS: ASSESSING COMPLIANCE WITH EXISTING GUIDELINES IN SEVEN ITALIAN HOSPITALS.

Purpose: Oncology nurses and pharmacists who work in oncology settings are at risk of exposure to antineoplastic drugs (ADs). Protection from AD exposure depends on safety programs established by employers and followed by workers. That is why adherence to guidelines should be evaluated routinely. The main goal of this study was to assess the compliance with existing guidelines in seven Italian hospitals, through an effective monitoring program, including environmental and biological measurements.

Methods: In order to verify continuing compliance, periodic assessments were scheduled. All employees involved in the preparation and administration of ADs were monitored. Urine samples collected at the beginning and at the end of the work shifts as well as wipe tests, pads and the internal side of the gloves, were analyzed for a number of drugs. To assess exposure to cyclophosphamide (CP), ifosfamide (IF), 5-fluoruracil (5-FU), taxol (TAX), anthracyclines (DOXO, DAUNO, EPI and IDA), gemcytabine (GCA), and platinum-compounds, highly sensitive and specific analytical methods had been developed and validated. The external contamination of drug vials supplied by pharmaceutical manufacturers, was also evaluated. Repeated annual measurements were carried out over a four-years period in order to identify whether current practices are sufficient for preventing exposure or changes need to be made.

Results: Virtually all biological samples were found to be below detection limits (LODs = 0,1 f^g/L for CP, IF, TAX, DOXO, DAUNO, EPI and IDA). A progressive, significant decrease in workplace contamination was observed as well. These results are consistent with the findings from similar studies conducted in other Italian hospitals, where adherence to guidelines is rather high. It was also observed that conducting periodic investigations increases staff awareness of the possible contamination due to ADs handling.

Conclusions: An investigation conducted in seven Italian hospitals demonstrated a dramatic reduction in the percentage of urine samples with measurable levels of ADs and the concentration of the drugs in urine following use of proper devices and protective equipment. Following recommended guidelines on AD preparation and handling is essential for protecting both the environment and the operators.

88

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Valli A.,
Rocchi L.,
Baldi L.,
Papa P.,
Locatelli C.

In: *Atti del XXVII International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT); Atene (Grecia), 1-4 Maggio 2007; 351.*

ANALYTICAL IDENTIFICATION OF ORAL ANTIDIABETIC MISUSE IN AN EMERGENCY SETTING.

Objective: Sulphonylureas and biguanides (phenformin and metformin) are the two classes of oral antidiabetic drugs usually prescribed in diabetic patients. Sulphonylureas act as hypoglycaemic agents stimulating endogenous insulin production; biguanides are antihyperglycaemics that enhance the action of insulin. In Italy, chlorpropamide or glibenclamide are associated with biguanides in pharmaceutical preparations. Analytical identification and quantification can be useful in cases of oral antidiabetic misuse in the emergency setting.

Methods: Cases of antidiabetic misuse in patients admitted during a 36 months period to the emergency department (ED) for hypoglycaemic crisis of undetermined origin were retrospectively studied. Antidiabetic analysis was performed in biological fluids: serum screening for sulphonylureas was made with a method based on liquid/liquid extraction and HPLC-UV separation/detection. Phenformin was analysed using HPLC-UV: the serum was deproteinized, while urine was directly injected. Metformin was first derivatized in serum and urine, then submitted to liquid/liquid extraction and GC-MS examination.

Results: Five cases of suspected oral antidiabetic misuse were included. All the patients were admitted for hypoglycaemic crisis (glycaemia range: 17-30 mg/ dl). Clinical examinations never revealed pathological causes, so toxicological analysis, in particular sulphonylurea screening, was requested of the analytical toxicology laboratory. Only one patient had a history of diabetes, but no one was known to be on therapy with oral antidiabetics; in two cases a psychiatric disease was present in the history. Three cases resulted positive for glibenclamide in serum: one of them was positive also for metformin and another one for phenformin in serum and urine. Two cases tested negative for sulphonylureas and biguanides in blood, but positive for metformin in urine. Therapeutic or subtherapeutic concentrations were always detected.

Conclusion: The suspected antidiabetics misuse has been confirmed by the toxicology laboratory analysis in all the patients. The presence of glibenclamide clearly correlates to the hypoglycemic crisis in three patients. The presence of biguanides in the urine of two patients can be likely interpreted as an assumption of an associated pharmaceutical preparation since biguanides alone normally don't cause an important decrement in blood glucose. The analytical methods adopted are suitable to reveal sub-therapeutic concentrations of sulphonylureas. If the misuse is related to associated preparations, the analysis of metformin and phenformin is a useful diagnostic tool in case of delay between drug consumption/hypoglycemic crisis and sample collection, since the extensive metabolism of most sulphonylureas makes their evaluation difficult in biological samples collected several days after drug ingestion.

89

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIAValli A.,
Rocchi L.,
Papa P.,
Locatelli C.In: *Atti del XXVII
International Congress
of the European
Association of Poisons
Centres and Clinical
Toxicologists (EAPCCT);
Atene (Grecia),
1-4 Maggio 2007;*
45; 351.

RELEVANCE OF ANALYTICAL IDENTIFICATION OF BIGUANIDE POISONINGS IN EMERGENCY SETTINGS.

Objective: Metformin and phenformin are prescribed in Italy as monotherapy or associated with sulphonylureas. Cases of biguanide poisoning can be suspected in the emergency setting, but analytical confirmation is not always accessible because of the unavailability of simple and rapid analytical methods. *Methods:* The analytical results of eight cases of biguanide poisoning obtained in the emergency setting have been evaluated. The serum quantification of the drugs was performed with a method based on protein precipitation and HPLC-UV.

Results: At admission, serum metformin concentration was 10.4 mcg/ml (therapeutic: 0.18-1 mcg/ml) in one case of intentional overdose, whereas higher serum levels (between 60 and 100 mcg/ml) were detected in 6 of the 7 cases of poisoning secondary to accumulation as a consequence of renal impairment during chronic therapy. The seventh case of accumulation was related to phenformin, with a serum level of 0.38 mcg/ml (therapeutic: 0.16-0.24 mcg/ml). In four cases sulphonylureas were also present. All patients presented with significant lactic acidosis (lactate range 18-33 mmol/l, pH 6.62-7.24). In the case of attempted suicide the renal function was normal, the patient was treated with sodium bicarbonate and the drug was eliminated over 36 hours. The patients with metformin accumulation during treatment underwent dialysis, and the one with a serum level of 100 mcg/ml died. The phenformin-poisoned patient was treated with sodium bicarbonate and the metabolic acidosis resolved in 12 hours.

Conclusion: In our cases metformin levels above 10 mcg/ml were related to important toxic effects, and the appearance of renal impairment during chronic therapy was the most relevant cause of severe biguanide toxicity. Serum phenformin level of 1.5 times greater than the normal range is related to severe lactic acidosis. The method we adopted is suitable in emergency for the diagnosis of acute poisoning, both in attempted suicide and in accumulation during treatment. It is very simple, fast (results are available in 30 min) and has sufficient specificity and sensitivity in case of toxic concentrations.

90

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIAVitelli N.,
Chiodini A.,
Somaruga C.,
Turci R.,
Minoia C.,
Colosio C.In: *Atti del 7th International
Symposium on Biological
Monitoring; 2007; 140.*

BIOLOGICAL MONITORING OF OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE TO ANILIDE AND DICARBOXIMIDE PESTICIDES.

Purpose: Dicarboximide fungicides (DF) are widely used on vines, fruit and vegetables, and anilide herbicides (AH) are used to control weeds on hard surfaces, such as, roads, railway tracks, paths, and to control weeds in crops, forestry, ornamental trees and shrubs, pineapples, sugar cane, cotton, alfalfa and wheat. AH and DF have been associated to adverse health effects that include possible carcinogenicity as well as endocrine disruption, immune and nervous system disorders. That is why human exposure assessment is timely and necessary. This study has been carried out with the aim of assessing exposure to AH and DF in a sample of the general Italian population and in a group of agricultural workers. Secondly, we aimed to define tentative reference values for these compounds.

Methods: A total of 186 subjects participated in this study. Thirty three of them were pesticide applicators exposed to propanil, while 153 had no history of occupational exposure to pesticides. Information on age, gender, site of residence, dietary habits and health conditions, were collected through a very detailed questionnaire. Urine samples were analyzed for 3,4-dichloroaniline and 3,5-dichloroaniline, which are considered as the two major metabolites of AH and DF. Spot samples were collected in the morning (second void of the day) from the general population, whereas three samples (before and after Propanil application and the morning after the application) were obtained from the occupationally exposed subjects. Analyses were performed by gas chromatography coupled to mass spectrometry (GC-MS).

Results: Detectable levels of 3,4-dichloroaniline and 3,5-dichloroaniline were found in 81.7% and 98.7% of the general population, with mean urinary levels of 0.65 „b 1.27 f°g/L and 0.63 „b 1.01 f°g/L, respectively. In the exposed workers, baseline metabolite concentrations were of the same order of magnitude as the general population. After pesticide application, an increase by three orders of magnitude was observed, and urinary levels up to 432.3 „b 545.9 f°g/L, were measured. The highest values were observed in workers using tractors without air-conditioning or responsible for machinery maintenance and cleaning.

Conclusions: 3,4-dichloroaniline and 3,5-dichloroaniline are biological indicators suitable for monitoring occupational and environmental exposure to DF and AH. Mean urinary levels were found to be about 0.6 f°g/L for both the analytes. Moreover, our data suggest that most of the human population is exposed to these pesticides, but further studies are necessary to better define the possible sources of exposure.

91

Comunicazione scientifica pubblicata su atti congressuali

Istituto di
PAVIA

Yacoub M.R.,
Perfetti L.,
Pignatti P.,
Moscato G.

In: *Allergy*; 2007; 62;
279-280.

USEFULNESS OF INDUCED SPUTUM IN INVESTIGATING OCCUPATIONAL ASTHMA WITHOUT NON SPECIFIC BRONCHIAL HYPERRESPONSIVENESS TO METHACHOLINE: A CASE REPORT.

Background of the Study: Current international guidelines suggest stopping investigations of occupational asthma (OA) in the case of normal non specific bronchial responsiveness (NSBH) in a subject currently exposed to the suspected agent(s) in the workplace.

Aim: To evaluate the usefulness of assessing airway inflammation by means of induced sputum (IS) in the case of a negative NSBH in the diagnostic pathway of OA.

Subject and Methods: We describe the case of a 33-years-old atopic, ex smoker man referred to our unit in April 2006 for evaluation of work-related respiratory symptoms. He had been working as a technician in an electric industry for a 6 months before the investigations. Dyspnoea, productive cough, chest tightness and wheezing appeared a few days after beginning this job. Stop-resume test was positive. He had never complained of respiratory symptoms before. In addition to common diagnostic tools used in the flowchart of OA, IS before and after specific inhalation challenge (SIC) was performed.

Results: At baseline spirometry, reversibility test, NSBH to methacholine (Mch) and PEF measurements were normal. The only abnormal finding at this stage (before SIC) was the increase in eosinophils count (11.7%, normal value < 2%) in IS obtained 60 h after the last exposure in the workplace. After a control day with isobutylacetate. SIC with cyanoacrylate carried out with occupational method revealed a late response (16% fall in FEV₁ 300 min after the end of exposure). Ten hours after the challenge, also a 25% fall in PEF was observed. The day after SIC Mch challenge showed normal responsiveness (PD₂₀>2376ug) whereas IS cellular analysis showed a significant increase in total cellular count (2640 cells/mg post-SIC vs. 1320cells/mg pre-SIC) and an increase in eosinophils (54.5%). The diagnosis of OA due to cyanoacrylate was made.

Conclusions: Our case underlines the importance of assessing airway inflammation by means of IS in the diagnostic pathway of OA when NSBH to Mch is normal, before excluding the possibility of OA.