radionuclides origin and abundance on different environmental matrices. Following, potential applications on environmental studies will be presented, and, finally, results obtained on several project developed by the Instituto de Radioproteção e Dosimetria/Comissão Nacional de Energia Nuclear (IRD/CNEN/MCT) and by the Chemistry Department of PUC-Rio. — (*May 24, 2002*) .

CLINICAL STUDIES – GENERIC MEDICINES

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Presented by HELIO B. COUTINHO

Clinical testing is not the only way to discover drug effects on people. That is the reason controlled clinical trials are the only legal basis for central regulatory agencies in each country, such as FDA, to conclude that a new drug has clinical effectiveness for a drug or biologic. Before clinical testing begins, researchers analyze the drug's main physical and chemical properties in the laboratory and study its pharmacological and toxic effects in laboratory animals. On the other hand, bioequivalence studies are the clinical test used, most often, when a sponsor proposes manufacture a generic version of an approved off-patent product. The law 9.787 (1999), established the legal basis for the institution of generic drugs in Brazil. Our research group started clinical trial and bioequivalence studies, with collaboration of the Public Pharmaceutical Laboratory of Pernambuco State (LAFEPE), the Brazilian official company to pioneer the development of medicines for AIDS and herperviruses treatment, between 1995 to 1998, even before the establishment of generic policy in Brazil. In 1997 and 1998, LAFEPE was ranked in 21st market position vs. all public and private pharmaceutical laboratories in Brazil. The Aids medicines at a low cost increased the production and sales, and were the main reason of such inedited result.

As a result of the studies developed, the following medicines were introduced to the Brazilian market by LAFEPE: stavudine and zidovudine (AZT) capsules, ganciclovir injectable, lamivudine + AZT, didanosine, lamivudine, and zalcitabine tablets. The result showed bioequivalence for lamivudine tablets (RT) as the 90% CI for both Cmax (99,7) and AUC0-12 (96,7) geom. mean ratios lie within the 80-125% interval. On AZT + DDI therapy the plasma HIV RNA levels decreased $> 0,5$ log after 30 days. The ganciclovir clinical study showed similar results in reference product by the control of retinitis in Aids patients infected with CMV. The stavudine and zalcitabine clinical study demonstrated no adverse effects reported and biochemical parameters remained unchanged and within the reference range. The pharmacokinetics parameters found for AZT + Lamivudine tablet were: AUC0-12 (8975 e 12.189ng.h/ml); Cmax (7.330 e 3.610 ng/ml) respectively, similar to the reference medicine. — (*May 24, 2002*) .

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BACTERIOLOGICAL LARVICIDES OF DIPTERAN DISEASE VECTORS

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The bacteria *Bacillus sphaericus* (*Bs*) and *B. thuringiensis* serovar. *israelensis* (*Bti*), display toxic action on mosquitoes and black flies, important vectors of man disease, acting as per os larvicides. These sporulating bacteria show a major advantage over synthetic insecticides: selectivity due to the specific mode of action. *Bs* is toxic against some species of Culicidae while *Bti* is also highly toxic against Simuliidae.

Both bacteria produce, during the sporulation, crystals, which contain protoxins. *Bti* crystals contain four polypeptides of 123-, 135-, 72- and 28-kDa, respectively called Cry4A, Cry4B, Cry11A and CytA. For *Bs*, crystals contain a toxin (Bin) made of two polypeptides of 42- and 51-kDa, called BinA and BinB, respectively. The mode of action of these proteins on larvae involves the ingestion of crystals and spores in suspension in water. Inside the midgut lumen, under the action of the alkaline pH and proteinases, protoxins in the crystals are solubilized and activated. Released toxins bind to apical microvilli of midgut cells, then cytopathological alterations are observed in midgut cells, leading to the death of larvae. Those toxins need to act in synergy to display the full toxicity and also bind to specific receptors in the larval midgut. Recently, the receptor of the Bin toxin of *Bs* in *C. pipiens* larvae was identified as being an α-glucosidase of 60 kDa.

Bti and *Bs* based larvicides have been produced and successfully used in vector control programs throughout the world. *Bti* has been mostly used to control species

of *Simulium* and *Aedes*, vectors of onchocerciasis and dengue, respectively, while, *Bs* is very effective for controlling *Culex* species, vectors of filariasis and encephalitis. Data from the operational use of microbial larvicides in several countries, in the past two decades, have confirmed the effectiveness of *Bti* and *Bs* and their safety to non-target species. On the other hand, *Culex* populations intensively sprayed with *Bs*, can display resistance. Data shows that *Bs* should be used into integrated programs with other control agents such as *Bti*, in order to avoid these phenomena. Resistance is unlikely to appear towards *Bti* due to its multiple toxins. — (*May 24, 2002*) .

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X-RAY DIFFRACTOMETRY APPLIED TO THE COMPARATIVE STUDY OF PROCESSES OF FORMATION OF AUTOMOTIVE BATTERIES

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Presented by VALDEREZ P. FERREIRA

X ray diffraction was applied to the investigation of the main steps in lead acid battery production (mixing, soaking and formation) in order to improve manufacturing conditions and to contribute with a theoretical understanding of these processes.

In the first step, mixing, the following results were obtained: (a) liquid nitrogen freezing of the paste was effective; (b) the reaction was instantaneous; (c) it is directly related to the amount of acid added.

In the soaking step, plates with a high content of total sulfate display a final monobasic lead sulfate content bigger than those displayed by plates with low content of total sulfate. In order to explain this behavior, two hypotheses are proposed: (a) 3BS could lead to monobasic sulfate crystallization; and (b) 1BS initially present in the plates could act as seeds for further crystallization. Crystal sizes were also followed as a function of time during the soaking period, demonstrating the possibility of extending the use of X-ray diffraction in the observation of crystal sizes in this and any other step of battery production.

In continuous current formation it was observed that higher temperatures (60^oC) are favorable, affected by an increase in current and especially by the interaction: increase in current vs. increase in density. The best results of plate formation were obtained with plates rich in tribasic lead sulfate. It was found that the total charge used in the industry is too high and a reduction of up to 43% of the charge yields excellent results, with PbO_2 contents as high as 92% with an average of 80%.

A laboratory test of pulsed formation showed that longer time is the main factor in order to achieve better results, moreover longer pulses in experiments with short times also yield higher contents of PbO_2.

In a comparison of both formation schemes it was observed that pulsed formation was more efficient, with respect to total PbO_2 obtained, with plates richer in tetrabasic sulfate. In continuous formation, under the same experimental conditions, no tetrabasic sulfate remains unformed. — (*May 24, 2002*) .

OXYGEN ISOTOPES INTERNAL EQUILIBRIUM IN MAGMATIC EPIDOTE-BEARING GRANITOIDS

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In this study we present oxygen isotope compositions of mineral separates from three metaluminous epidote-bearing granitoid series from northeastern Brazil.

Zircon has an overall $\delta^{18}O$ variation of $\sim 5‰$, ranging from $5.72‰$ to $10.30‰$, but is very homogenous within a single pluton. The highest values of $\delta^{18}O$ (zircon) ($9.88‰ \pm 0.35‰$; n = 13 samples) are for the calc alkalic granitoids, which are slightly, but significantly higher than those for high-K calc-alkalic granitoids ($9.10‰ \pm 0.41‰$; n = 19 samples) with little overlap. Values for these granitoids greatly differ from the average for the shoshonitic granitoids ($7.43‰ \pm 0.19‰$; n = 5 samples), and from that for the São Rafael pluton, a high-K calc-alkalic granitoid ($5.92‰ \pm 0.26‰$; n = 9 samples). These differences repeat for the other analyzed minerals, with little overlap of values. There is a good positive correlation between mineral pairs in the three series, although quartz-epidote and zircon-epidote fractionations are higher than predicted for equilibrium at magmatic temperatures. Measured mineral-mineral fractionations suggest continuous sub-solidus inter-mineral isotope exchange among all minerals except zircon. Calculated $\delta^{18}O$ (magma) values using whole rock SiO_2 contents and $\delta^{18}O$ (zircon) values are up to $1‰$ lower that those