significant increase in concentration at this depth interval at two stations. Five of the six measurements between 500 and 1500 meters showed cesium concentration substantially higher than the local surface concentrations; and the mean for this depth band is more than 14 percent higher than the mean for all surface concentrations.

Slight maxima have been reported at depths of 500 to 1500 meters for other trace elements; for example, bulges in the profile of the concentrations of radium and uranium have been reported (*6*), amounting to about 10 percent of the surface value. Concentrations of such nutrients as nitrates and phosphates that are consumed by marine microorganisms often exhibit maxima at these depths. One common explanation is that degeneration of particulate size takes place at these depths, so that the rate of descent decreases. A maximum in cesium concentration at these depths, therefore, suggests that downward transport of cesium by organisms should not be overlooked. There is also the possibility that the penetration of fallout cesium may be influenced by attachment to organisms or to inorganic particles carried by them. Certainly, more sampling of natural cesium and fallout cesium at the intermediate depths should be made to resolve this question.

T. R. FOLSOM
Scripps Institution of Oceanography, La Jolla, California

C. FELDMAN
T. C. RAINS
Oak Ridge National Laboratory, Oak Ridge, Tennessee

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Nicotinic Acid Analogs: Effects on Response of Chick Embryos and Hens to Organophosphate Toxicants

Abstract. *Embryonic abnormalities are known to be induced in chick embryos when they are injected with certain organophosphate insecticides prior to incubation. The marked teratogenic effects of Bidrin [3-(dimethoxyphosphinyloxy)* N,N-*dimethyl-cis-crotonamide] can be alleviated by many analogs of nicotinamide and nicotinamide adenine dinucleotide. Successive hydroxylation and* N-*dealkylation of Bidrin in the egg are not greatly altered by injection of nicotinamide. The delayed neurotoxicity in adult hens after administering tri-*o-*cresyl phosphate is also partially relieved by administering certain nicotinamide analogs.*

Certain biological effects of toxic organophosphates appear to be unrelated to the inhibition of acetylcholinesterase activity in the nervous system. These include, among others, a teratogenic effect in the developing chick embryo (*1*, *2*) and a neurotoxicity with associated axonal degeneration and demyelination in certain tracts of the central and peripheral nervous system as found in hens in which the syndrome has been studied most extensively (*3*). The teratogenic effect of malathion (*S*-[1,2-bis-(ethoxycarbonyl)ethyl] *O*,*O*-dimethyl phosphorodithioate) with chick embryos was potentiated by EPN (*O*-ethyl *O*-*p*-nitrophenyl phenylphosphonothioate), TOCP (tri-*o*-cresyl phosphate), and 2-ethylhexyldiphenyl phosphate (*2*). Paralysis was observed in some chicks hatched from eggs that had been injected with 10 mg of TOCP (*1*). Teratogenic effects in chick embryos are also produced by certain carbamates (*2*, *4*), and nicotinamide offers near complete protection against such action of eserine (*5*). No studies have been reported on attempts to alleviate the teratogenic effects of organophosphates with selected biochemicals, but extensive trials in which prophylactic agents for the neurotoxic effect were sought have not been successful (*6*).

A series of vinyl phosphates was injected at the rate of 1 mg per egg into the yolk sac of fertile eggs prior to incubation according to a described procedure (*1*). The hatching ability and the condition of the chicks on hatching, or the appearance of the embryos at 21 days if hatching was unsuccessful, were then observed. Some of the vinyl phosphates always caused marked teratogenic effects. The condition of the embryo in the most extreme cases included complete lack of feathers, parrot beak, shortening and deformation of the legs and spine, edema, growth retardation, and, rarely, syndactylia; all these symptoms have been reported with certain other organophosphates (*2*). Thirteen vinyl phosphates of the type $(R_1O)_2P(O)OC(R_2) = C(R_3)(R_4)$ were examined (*7*). The four most active materials were (R_1, R_2, R_3, R_4): Me, Me, H, C(O)NMe_2 or Bidrin; Me, Me, H, C(O)NEt_2; Et, Me, H, C(CO)NMe_2; and Me, Me, H, C(O)NHMe. The teratogenic effect was less marked with Et, H, H, Cl and Me, Me, Cl, C(O)NMe_2, and even higher doses were required for activity with Et, Me, H, C(O)OEt and Me, Me, Cl, C(O)NEt_2, or phosphamidon. The following insecticides were inactive, even when injected at the rate of 10 mg per egg: Me, Me, H, C(O)OMe or mevinphos; Me, Me, H, CH(Me)Ph or Ciodrin; Me, H, Cl, Cl, or dichlorvos; Me, OMe, Cl, Cl; and Et, 2,4-Cl_2Ph, H, Cl. Also inactive were a variety of possible phosphorus-containing and nonphosphorus-containing hydrolysis products of Bidrin. Teratogenic effects were occasionally observed when 100 μg per egg of the *cis*-crotonamide isomer of Bidrin was injected, and always when 300 μg or more of Bidrin was injected per egg. The severity of effect increased progressively with higher doses. The effect was evident when Bidrin was injected during the first 6 days of incubation, but not after 9 days of incubation.

A number of vitamins and other biochemicals were assayed by simultaneously injecting 1 mg of Bidrin and 1 mg of each substance per egg prior to incubation to ascertain their possible effects in relieving the teratogenic symptoms. Only nicotinic acid analogs or potential precursors thereof were active, many of them yielding embryos normal in appearance at 21 days although hatching was usually unsuccessful. As little as 30 μg of nicotinic acid or nicotinamide per egg was active. Nicotinamide adenine dinucleotide (NAD) and its 3′-phosphate in both their oxidized and reduced forms were very active, as were certain analogs of NAD and nicotinic acid esters and amides.

When Bidrin was injected prior to incubation, the nicotinic acid derivative could be injected at any time during the first 4 or 6 days of incubation with great effectiveness, but after about 10 days of incubation the nicotinamide did not alter the teratogenic action of Bidrin. On simultaneous administration of Bidrin and nicotinic acid or nicotinamide at any time between 0 and 12 days, no teratogenic effects were observed.

Bidrin, labeled with both phosphorus-32 and *N*-methyl-C^{14}, was injected at the rate of 1 mg per egg into the yolk on the 4th day of incubation with and without 1 mg of nicotinamide. Only the *cis* crotonamide isomer was used as it was much more potent than the *trans* crotonamide in effecting a teratogenic action. Bidrin was mostly hydrolyzed within a few days, but intermediate nonhydrolytic metabolites were formed. These consisted of Me, Me, H, C(O)NHMe; Me, Me, H, C(O)$NHCH_2OH$; Me, Me H, C(O)NH_2; and possibly also trace amounts of the initial hydroxylation product, Me, Me, H, C(O)$NMeCH_2OH$ (*8*). The concentration of Bidrin, and of these products from successive hydroxylation and *N*-dealkylation, did not vary greatly either in the egg or the embryo as a result of administering nicotinamide. These analyses were made at the 6th, 8th, and 10th days of incubation. Although the metabolism of Bidrin was unaffected, the nicotinamide almost completely reversed the teratogenic effect.

The neurotoxicity of TOCP in adult hens was studied after oral administration of 0.5 ml of TOCP per kilogram of body weight. Analogs of nicotinic acid were injected intraperitoneally, 0.25 to 8 mmole/kg daily, starting 2 days before the administration of TOCP and continuing through 7 days afterward. Some of these analogs prolonged the delay period—that is, the period before the appearance of symptoms—from the 10th day to the 12th or 13th day after the administration of TOCP, and the final severity of the symptoms as determined on the 21st day was much less in such cases. Marked ataxia and general debilitation could be alleviated, sometimes to the point of only mild weakness in the legs. Nicotinamide, 2 to 8 mmole/kg per day, and phenyl nicotinate, 1 to 2 mmole/kg per day, were the most effective. Less effective or inactive were the following compounds (*7*): nicotinic acid and its Me, Et, Pr, *i*-Pr, Bu, Hex, benzyl, and guaiacyl esters; the *N*-substituted nicotinamide analogs with mono- Me, Et, or benzyl and di- Me or Et amide substituents; and 3-pyridyl compounds with Me, CH_2OH, CHO, CN, and C(O)Me radicals.

Nicotinamide and certain analogs are known to protect chick embryos from the teratogenic effects induced by eserine, insulin, sulfanilamide, 6-aminonicotinamide, and 3-acetylpyridine, and to forestall or lessen the effects of pilocarpine and other teratogenic compounds (*5*, *9*). Growth inhibition of certain protozoa by thalidomide was counteracted by nicotinamide and NAD (*10*). The development of glossitis and possibly also polyneuritis upon prolonged therapy with large doses of thalidomide in humans was controlled by the prophylactic use of vitamin-B complex (*11*). Some protection is also offered by nicotinamide and certain analogs against EPN poisoning in mice, guinea pigs, and rats, possibly because they prevent the inhibition of tissue cholinesterase activity (*12*).

The action of nicotinic acid analogs in alleviating the effects of organophosphates might be related to their having an effect on the metabolism of the toxicant, a protective action on the cholinesterase or other active site, or to their providing adequate amounts of a pyridine nucleotide coenzyme to allow a critical enzymatic reaction blocked by the organophosphate to function almost normally through this or an alternate pathway. The experiment in which phosphorus-32 and *N*-methyl-C^{14}-labeled Bidrin was injected into chick embryos failed to support the first hypothesis. The other two hypotheses are under investigation.

J-C. ROGER*
H. CHAMBERS*
J. E. CASIDA*

Department of Entomology, University of Wisconsin, Madison 6

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* Present address: Division of Entomology and Acarology, University of California, Berkeley 4.

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trans-2-Dodecenal and 2-Methyl-1, 4-Quinone Produced by a Millipede

Abstract. *An aldehyde,* trans-2-*dodecenal, heretofore known only from plants, has been identified in the defensive secretion of the spiroboloid millipede* Rhinocricus insulatus. *A second component, 2-methyl-1,4-quinone, was previously known from the secretion of related millipedes.*

The defensive secretions of arthropods are natural products of extraordinary chemical diversity (*1*). Even relatively closely related species may produce secretions of grossly dissimilar composition. Millipedes are a case in point. Some (order Polydesmida) produce a cyanogenic secretion (*2*), others (order Chordeumida) discharge a phenol-containing mixture (*3*), and still others (orders Julida, Spirostreptida, and Spirobolida) secrete *p*-benzoquinones (*4*, *5*). We received recently from Barro Colorado, Panama, a shipment of live *Rhinocricus insulatus* (Chamberlin) (*6*), a species of the Spirobolida, and hence one that could be expected to produce quinones. Although the secretion of this millipede did indeed appear to be quinonoidal (yellow color, ability to tan human skin), it nevertheless seemed worthwhile investigating, since its odor