A REVIEW OF GENERAL ACUTE TOXICITY STUDIES OF *INCIDE® PEST CONTROL INSULATION*

Prepared For

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June 8, 1998

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EXECUTIVE SUMMARY

Intertox, Inc. has extensive experience reviewing the general use and toxicity of boron-based products, and sodium polyborate in particular. A general review of boron-based compounds indicates that these compounds occur naturally in low concentrations in air, water, and soil and are of generally low toxicity. We review here six acute animal toxicity studies in which a boron-containing product,[1] called *InCide® Pest Control Insulation*,[2] was tested. The acute toxicity studies reviewed include those examining adverse health effects associated with contact with the product on the skin and eyes and through inhalation and ingestion. These studies appear to have been performed according to acceptable experimental protocols.

Four of the six studies reviewed indicate no observed adverse health effects from exposure of the test animals to *InCide® Pest Control Insulation.* A fifth study indicated temporary and minimal eye irritation when the product was placed under the test animals' eyelids. The sixth study, an oral toxicity study, successfully established the benchmark toxicity measure LD_{50} for the product, but only by treating animals with the pure active ingredient of *InCide® Pest Control Insulation*, sodium polyborate. The LD_{50} for sodium polyborate was estimated to be 3,339 mg/kg while that of *InCide® Pest Control Insulation* would be 16,370 mg/kg,[3] indicating that the products, as formulated, have lower toxicity than many competitive products, such as boric acid, and common substances, such as table salt. Further, test animal ingestion of *InCide® Pest Control Insulation* in the range of this amount was regarded by those conducting the study as impractical because of the bulkiness and of the product. Based on these reviews and assuming foreseeable circumstances of exposure during product application or occupation of a structure treated with *InCide® Pest Control Insulation*, we do not expect the product to cause adverse health impacts beyond those that are mild and temporary.

[1] Boron-containing material added to cellulose insulation contains 100% sodium polyborate. Animal tests cited herein were conducted using a cellulose insulation product that contained similar concentrations of sodium polyborate and shredded newspaper.
[2] The chemical load factor for *InCide® Pest Control Insulation* is approximately 23% sodium polyborate (Boron-10™) by weight.
[3] Since *InCide® Pest Control Insulation* contains at most 23% of the active ingredient (sodium polyborate), a comparison between the toxicity of the active ingredient and the material as a whole can be made by dividing the LD_{50} for the sodium polyborate by the fraction of sodium polyborate in the insulation (0.23). Hence 3,339 mg/kg ÷ 0.23 = 14,520 mg/kg. Note that we assume that the other ingredients in the insulation (i.e., cellulose) are not of toxicological significance if ingested.

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INTRODUCTION

InCide® Pest Control Insulation is an insulative construction material composed of primarily cellulose fiber materials and sodium polyborate. *InCide® Pest Control Insulation* is designed for use in commercial and residential buildings as insulation.

Many boron compounds exist naturally throughout our environment, and boron is an element commonly ingested on a daily basis in small amounts by humans. Such compounds, commonly found in soil, fruits and vegetables, and water, generally have low toxicity and pose little threat to human health unless great quantities are ingested or absorbed through damaged skin. In the following sections, several toxicity studies of *InCide® Pest Control Insulation* are reviewed and evaluated.

REVIEW OF ANIMAL TOXICITY STUDIES

Animal toxicity studies are performed to indicate whether a given compound is likely to be toxic to humans. For each study, test animals are exposed to high dosages of the test product and both behavioral and physical responses are studied. The species for each type of study was chosen based on its demonstrated sensitivity to a given type of exposure (e.g., New Zealand White albino rabbits are generally very sensitive to substances applied to the skin) and because of knowledge that the animal's biological means of processing such exposures is most likely similar to that of humans.

Given the difficulty and expense of conducting studies of long-term exposures, short-term, or "acute," toxicity studies are the most commonly performed. The principles described above apply to such studies; dosages are often extreme in order to produce obvious, observable effects. One of the most commonly measured observed effects of such an extreme exposure is death of the test animal. Survival rates in these extreme exposures are used to estimate a toxicity measure known as the "lethal-dose-50," or LD_{50}, defined as the dose of a compound that would be lethal for 50% of a group of test animals. Because individual test animals have differing capacities to survive exposure to a given compound, some being highly sensitive to exposure and some being relatively insensitive, this measure of lethality for half the test group has become a standard measure of acute toxicity. Additionally, acute toxic response to *Incide® Pest Control Insulation* was studied through skin and eye exposures and through ingestion and inhalation because a compound can have toxicity through some routes of exposure and not others.

To simplify application of toxicity values to humans, LD_{50}s are measured in mass of compound per mass of body weight, e.g., milligrams *InCide® Pest Control Insulation* per kilogram body weight of the subject. LD_{50} values have been determined for many chemicals. Therefore, given the results of the studies reviewed here, toxicity comparisons can be made between *InCide® Pest Control Insulation* and many other products and compounds using this value.

Each of the six acute animal studies reviewed here was conducted in 1986 by American Biogenics Corporation in Decatur, Illinois, and appears to have been performed in conformity with the Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) Good Laboratory Practice regulations. These regulations require, among other practices, the humane treatment of animals during testing. Each study was examined for its experimental protocol, in part because the studies are 10-years old. Each study report provides substantial information about the procedures and protocols used, which were deemed to be adequate.

The following subsections provide descriptions of the studies and summarize the studies' findings and our opinion regarding the potential for *InCide® Pest Control Insulation* to cause adverse health effects in humans.

ORAL TOXICITY STUDY

The purposes of an acute oral toxicity test are to 1) estimate acute toxicity, 2) identify organs that are affected by compound exposure and the toxic effects, 3) determine the reversibility of the toxic effects, and 4) provide a dose range for further studies, if necessary.[4] In this test, as in most tests of this type, the test animals were rats.

InCide® Pest Control Insulation could not be tested directly for acute oral toxicity because the bulkiness of the product made it impractical to feed the test animals enough product to induce toxic effects. Instead, through consultation with the EPA, this test was conducted on the active constituent of *InCide® Pest*

[4] Klaassen, 1996.

Control Insulation, sodium polyborate,[5] thus avoiding the bulky paper-fiber material (deemed non-toxic) found in the insulation.

Using groups of five rats, including both males and females, American Biogenics Corporation tested the following one-time dosages of the sodium polyborate: 2,818, 3,548, 3,758, 3,981, 4,467, and 5,000 milligrams per kilogram of animal weight (mg/kg). Based on the study calculations, these doses of sodium polyborate would be toxicologically equivalent to the following doses of *InCide® Pest Control Insulation*: 12,809, 16,127, 17,082, 18,096, 20,305, and 22,727 mg/kg.[6] Given the study results and the calculation noted above, the oral LD_{50} of *InCide® Pest Control Insulation* was calculated to be 15,177 mg/kg. Thus, the estimated lethal oral dose for an average (70 kg) adult human would be roughly 1.1 kg, or 2.3 lbs. Because *InCide® Pest Control Insulation* has lower concentrations of boron compounds, we expect the LD_{50} to be greater (*InCide® Pest Control Insulation* would be less toxic with estimated LD_{50}s of 16,370 mg/kg).

proved to be appropriate for developing an LD_{50}. This indicates no need for additional testing outside of the range of Postmortem examination of rats treated with fatal doses of sodium polyborate revealed abnormalities including discoloration of various tissues and moderate deformation of kidney and liver tissues. No such symptoms or conditions were noted in rats surviving the test exposure to the product. Additionally, based on the mortalities within the test groups, the range of product amounts administered to the test animals tested exposures.

DERMAL TOXICITY STUDY

The purposes of an acute dermal toxicity test are to 1) determine if exposure to a large dose of a compound can result in absorption through the skin in quantities great enough to result in an acute toxic effect, 2) determine the reversibility of the toxic effects, and 3) provide a dose range for further studies, if necessary. For those compounds that cross the skin in sufficient quantities and cause death, a dermal LD_{50} can be calculated.

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[5] Letter from Ms. Sandra Smith, September 9, 1986.

[6] Since *InCide® Pest Control Insulation* contains, at most, 23% of the active ingredient (sodium polyborate), a comparison between the toxicity of the active ingredient and the material as a whole can be made by dividing the doses of sodium polyborate by the fraction of sodium polyborate in the insulation (0.23). For example, in the case of the LD_{50}: 3,339 mg/kg (for males and female rats combined) ÷ 0.23 = 14,520 mg/kg for *InCide® Pest Control Insulation.* Note that we assume that the other ingredients in the insulation (i.e., cellulose) are not of toxicological significance if ingested.

In this test, as in most tests of this type, test animals were New Zealand White albino rabbits and their exposure to the test product was for 24 hours. *InCide® Pest Control Insulation* toxicity was tested on five male and five female rabbits. Fur from approximately ten percent of the surface of the rabbit was shaven and 2000 milligrams of the test product per kilogram of body weight was applied to the shaven area. Following the exposure period, the site was wiped, and the rabbits were monitored for adverse health effects. No adverse health indications were associated with these exposures. Because there were no adverse health effects or deaths, the authors used the largest dose category for this type of study and concluded "the acute dermal LD_{50} was considered to be greater than 2 grams per kilogram of body weight."[7] Thus, the estimated lethal dermal dose for an average adult human would be some level greater than 1/3 lb.

PRIMARY DERMAL TOXICITY STUDY

The purposes of a primary dermal toxicity test are to 1) determine if exposure to a large dose of a compound can irritate skin, 2) determine the reversibility of the irritation, and 3) provide a dose range for further studies, if necessary. In this test, as in most tests of this type, test animals were New Zealand White albino rabbits and their exposure to the test product was for 4 hours. Fur was shaven from an area of six rabbits' backs and 500 milligrams, the maximum practical amount, of *InCide® Pest Control Insulation* was applied to each of the shaven areas. Substances that can irritate skin cause the following signs: none, reddening, swelling, and, in some cases, the development of lesions. A scale, called the Primary Irritation Scale, ranging from 0 (no effects) to 8 (most severe), is used to measure dermal irritation. In repeated observations during 72 hours after application, *InCide® Pest Control Insulation* caused only minimal irritation of treated skin in three of the six animals tested. Therefore, it was given a ranking of 0 on the Primary Irritation Scale and deemed non-irritating.

PRIMARY EYE IRRITATION STUDY

Primary eye irritation studies are conducted to 1) observe the effect that large doses of a compound have on the eyes and body of a rabbit, 2) determine the reversibility of the toxic effects, and 3) provide a dose range for further studies, if necessary. In this test, as in most tests of this type, test animals were New

[7] Smith et al., July 28, 1986, Acute Dermal Toxicity…

Zealand White albino rabbits. One eye of each of six rabbits was treated with 100 milligrams of *InCide® Pest Control Insulation* and test animals were observed repeatedly during the following 72 hours for adverse effects.

Health effects can range from no effect or reversible adverse effects (e.g., redness of eye structures, swollen iris) to irreversible damage to the eye (e.g., clouding of the cornea, corrosive action to the tissues). The Primary Eye Irritation Scale is a rating system used to measure the degree of severity of a chemical exposure. The grading system is based on the effects of a test compound on three eye structures: 1) the cornea (the transparent structure that covers the iris and pupil), 2) the iris (which surrounds the pupil), and 3) the conjunctivae (the white of the eye). The scale ranges from 0 (no effect for any of the three structures) to 110 (severe effect in all three structures).

One hour after exposing the test animals' eyes to *Incide® Pest Control Insulation,* effects such as redness and discharge were noted. After 24 hours, these symptoms had substantially reduced and by 48 hours had completely reversed. Based on the study, *InCide® Pest Control Insulation* was considered to be minimally irritating to the eyes.[8]

DERMAL SENSITIZATION STUDY

The purpose of a dermal sensitization study is to determine the potential of a compound to sensitize skin. Sensitization is also called hypersensitivity or allergy. Sensitization is a complex biochemical phenomenon in which the body requires a previous exposure to elicit a reaction. In this test, as in most tests of this type, the test animal was the guinea pig and multiple treatments of the test product were applied to the shaven skin of guinea pigs over a period of 2 to 4 weeks. The test material was applied again 2 to 3 weeks after the last treatment and the skin was scored for swelling and redness. This last treatment is a low non-irritating dose. The skin is graded on a scale of 0 (no effects) to 4 (severe effects). No test animal was observed to have adverse health response to the initial or the final treatments, therefore, *InCide® Pest Control Insulation* "was not considered to be a contact dermal sensitizer."[9]

[8] Smith et al., July 11, 1986, Primary Eye Irritation…
[9] Smith et al., August 18, 1986, Dermal Sensitization Study…

FOUR-HOUR INHALATION TOXICITY STUDY

The purpose of a 4-hour inhalation study is to determine if breathing air with a high concentration of *InCide® Pest Control Insulation* can adversely affect the body or the respiratory system of an animal. In this test, as in most tests of this type, the test animal was the rat. One group of ten rats was continuously exposed for 4 hours to a time-weighted average concentration of 5.8 milligrams per liter (mg/l) dust aerosol of sodium polyborate dispersed in the atmosphere of a special exposure chamber. This was the highest airborne concentration the experimenters could create with the test product and equipment and is more than 350 times the workplace maximum recommended concentration for "inert or nuisance particulates."[10] Such a standard for non-toxic airborne materials is set in part because particles themselves can cause adverse effects (e.g., irritation and coughing).

Health effects of such an exposure can range from no adverse effects to death of the animal. If death occurs, an LC_{50} (lethal concentration in air for 50 percent of a test group) can be calculated. In this study, no animals died and no lesser adverse health effects were noted either during a 14-day observation period or during postmortem examinations. The experimenters concluded that an LC_{50} for sodium polyborate would be greater than an air concentration of 5.8 mg/l.[11] The equivalent concentrations *InCide® Pest Control Insulation* would be 25.22 mg/l.[12] Based on the signs of exposed animals in this study and all of the experiments as a whole, we would not expect adverse health effects at these high air concentrations of the products.

SUMMARY

The six animal studies reviewed herein provide fundamental information needed for assessing the inherent acute toxicity of *InCide® Pest Control Insulation*. The studies appear to have been performed using appropriate experimental protocols. These studies suggest that *InCide® Pest Control Insulation*, which contains the same boron ingredient as the tested product but at a lower concentration:

- was an estimated oral LD_{50} of 14,520 mg/kg;
- has a dermal LD_{50} of more than 2000 mg/kg;
- would not be a dermal irritant;

[10] ACGIH, TLV-TWA for particulates, not otherwise classifiable, 1994-1995.
[11] Newton et al., July 28, 1986, Four Hour Inhalation…
[12] Again, assuming *InCide® Pest Control Insulation* contains 23% sodium polyborate, the lower bound on the LC_{50} for the two compounds can be found by dividing the lower bound on the LC_{50} by 0.23.

- would be minimally irritating to the eyes;
- would not be a contact dermal sensitizer; and
- would have an LC_{50} of greater than 25 mg/l.

Four of the studies indicated no treatment-related adverse health effects whatsoever in the test animals. The acute oral toxicity study in rats (using only the active ingredient, sodium polyborate) indicated a steep dose-response curve for large doses between 2,818 and 3,981 mg/kg, indicating a closely defined range of toxicity for the population. This range of toxicity in rats indicates that the typical adult human lethal dose of *InCide® Pest Control Insulation* would be greater than approximately 2 lbs. For an average (15 kg) child, the amount would be about 8 oz. Both of these amounts are quite large and would not be expected to occur from an incidental ingestion during installation of the product or occupation of buildings with the product in place. Similarly, most domestic pets such as cats and dogs, would need to ingest impracticably large volumes of *InCide® Pest Control Insulation* to reach the average lethal dose for their body weights. The primary eye irritation study indicated short-term, minimal irritation as a result of introduction of the product into the test animals' eyes. This irritation is not surprising in light of the fact that the material is a solid and the particle masses themselves would cause some irritation, regardless of their chemical composition. However, recovery was complete within 48 hours of exposure, indicating that even minor adverse ocular effects were transitory.

CONCLUSION

InCide® Pest Control Insulation, with benchmark LD_{50} in excess of several grams per kilogram of body weight, can be classified as "relatively harmless."[13] Table salt, with an oral LD_{50} of about 4000 mg/kg,[14] is several times more acutely toxic.[15] Compared to other related household products and materials, *InCide® Pest Control Insulation* would be generally less toxic. For example, the LD_{50} for aspirin is 1500 mg/kg in male rats,[16] requiring substantially less to be ingested to produce a toxic effect than would be the case for *InCide® Pest Control Insulation.* The results of the reviewed studies indicate that the effects of exposures to *InCide® Pest Control Insulation* would be minor and temporary unless large doses were taken orally. Furthermore, ingestion of large doses, by weight, of these products would be impractical due

[13] Klaassen, 1996.
[14] Klaassen, 1996.
[15] Klaassen, 1996.

to the low density of the products. The minor and temporary health impacts of exposure to the product noted in the studies are consistent with exposure to non-toxic particulate matter, which can cause irritation when introduced under the eyelid and into the respiratory system. Beyond these effects, we expect no adverse health impacts to result from exposure under foreseeable product application and building occupation conditions.

[16] The Merck Index, 1996.

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