PERSPECTIVES ON *n*-PROPYL BROMIDE NEUROTOXICITY AND CARCINOGENICITY IN LIGHT OF NEW EVIDENCE AND NEW CHALLENGE

Adam M. Finkel, Sc.D., CIH
November 12, 2010

In my November 4, 2010 memorandum "Rationale for, and Derivation of, Performance Standards for *n*-propyl bromide (nPB) in Co-commercial Dry Cleaners," I reiterated my scientific opinion (as stated in my June 2010 report "Increased Toxicity and Carcinogenicity of *n*-propyl Bromide (1-bromopropane) Relative to Perchloroethylene") that nPB is a more potent animal carcinogen and human neurotoxin than Perc. I also provided quantitative risk-based derivations of various performance limits for nPB that are sufficiently protective of public health given current evidence. The nPB manufacturers have recently offered arguments, and supporting documents, in opposition to any regulation of nPB in dry cleaning; in part, their arguments rely on the claim that nPB is less toxic than Perc and less dangerous than my reports indicate. As addressed below, these arguments do not carry much if any weight in light of the totality of experimental and epidemiologic evidence. Furthermore, two new studies that have become available since June 2010 reinforce my earlier conclusions about nPB and its absolute and relative toxicity. In this report, I will refer to many of the opinions expressed by the manufacturers in the oral and written hearing record. However, the absence of a rebuttal to any specific claim made by the nPB manufactures should not be interpreted as my agreement with it.

I. Overview:

There will always be room for interpretation and uncertainty when evaluating qualitative, and especially quantitative, statements of hazard and risk. The historical record on environmental toxicants contains examples of "surprise" and changed opinions, but these generally involve cases where ostensibly "negative" studies turn out to have been insufficiently powerful and missed a harmful effect. It is possible that multiple positive studies linking exposure to a particular environmental toxicant to one or more

adverse health effects can all turn out to be incorrect. This, however, is unusual and depends on there being a plausible, well-described common flaw, something that the manufacturers have not attempted to put forward in the case of nPB.[1] Instead, they offer contrary interpretations of *some* of the experimental results, which even if they were compelling individually would not add up to enough evidence to overturn the larger body of observational findings.

Before discussing areas of controversy, however, I will briefly discuss the implications for setting quantitative performance standards, applicable to general-population exposures, if we were to begin only with observations about nPB toxicity that both the manufacturers and I *agree upon*. Even if we did not have ample evidence that nPB is more neurotoxic than the manufacturers acknowledge, I will show that standard methods of setting acceptable concentration limits, if based only on the manufacturers' interpretations of the science, should lead to a fairly stringent response by the City.

II. Quantitative Comparisons:

There is no disagreement that at "high" concentrations, even for occupational rather than continuous exposure, nPB is extremely dangerous. Dr. Stelljes ("White Paper" of August 20, 2010, page 10) opined that "At high concentrations (e.g., over 150 ppm), nPB can cause neurological impacts."[2] I agree that there is no doubt that levels in the 150 ppm range are unacceptably harmful. In the National Toxicology Program (NTP) rodent carcinogenicity bioassay, at less than half this level (62.5 ppm), nine out of 50 female mice developed lung cancers, compared to only 1 out of 50 in the control group—a 16 percent excess cancer rate (8 additional cancers out of 50), whereas federal, state, and local agencies strive in the general environment to reduce the excess to a 0.0001

---

[1] For example, if every positive epidemiologic study on a particular toxicant failed to control for a common variable that is correlated both with exposure and with effect, then the results may be misleading. If inhaling asbestos caused a craving to smoke cigarettes, then the relationship between asbestos exposure and lung cancer—if uncontrolled for smoking intensity—could be misleading.

[2] Similarly, Rich Morford (attorney for EnviroTech) stated at the August 12 public hearing (page 102, line 18 of the transcript) that exposing someone to 300-400 ppm of nPB would be "a criminal dose in my book." I agree with the spirit of this observation that 300-400 ppm is extremely dangerous; I assume Mr. Morford was using "criminal" simply as a pejorative of high level, rather than a strict legal conclusion.

percent (1 in 100,000) rate or less. The human neurotoxicity information also indicates that nPB exposure in the 50-100 ppm range and higher is extremely dangerous. All the case reports of irreversible neurological damage involve workers exposed at roughly these levels (see, e.g., Raymond and Ford (2007); Majersik et al. (2007); CDC (2008)—all full citations are available in my 11/4/10 report).

In my June 2010 report ("Increased Toxicity and Carcinogenicity of *n*-Propyl Bromide (1-Bromopropane) Relative to Perchloroethylene"), I stated that "the clear danger of nPB at higher exposures makes controlling nPB levels an important addition to the Philadelphia regulation." This statement does nothing more than assert the most fundamental scientific concept of dose-response: that *somewhere* below a concentration that is undoubtedly dangerous, a concentration must exist that is either below a true biological threshold (if there is one) or low enough that the probability of serious harm is acceptably small.[3] Therefore, it is natural that the only relevant question (either in appraising how dangerous nPB is in absolute terms or relative to Perc) is this one: at roughly what level **below** 150 ppm might exposure to nPB change from "dangerous" (or "criminal") to "acceptably safe"?

For non-carcinogenic endpoints (assuming, as in this case, that human data are available and therefore no additional animal:human adjustment is needed), there are three concentrations that can be used to set a Reference Concentration (RfC), or a Minimal Risk Level, that is believed to be reasonably health-protective: (1) a Frank Effect Level (FEL)—a concentration that clearly causes serious harm; (2) the Lowest Observed Adverse Effect Level (LOAEL)—a concentration that also causes demonstrable harm, but happens to be the lowest such concentration about which that can currently be said; and (3) the No Observed Adverse Effect Level (NOAEL)—a concentration below the LOAEL that is observed *not* to cause harm in a well-conducted study.[4] According to the

---

[3] In other words, contrary to Dr. Stelljes' misrepresentation of my report (on page 5 of his White Paper, he states that "[Finkel states] that nPB is toxic at all concentrations"), I simply reiterated what dose-response means: the lower the dose, the lower the response.

[4] As I emphasize below, no "negative" observation can be more useful than the study or measuring tool has power to detect harm. Therefore, a NOAEL should properly be interpreted as a level consistent with as much harm as would probably escape detection in the given setting. But for this discussion, I will treat the NOAEL as if it is truly a no-effect level, in order to give nPB the benefit of the doubt.

manufacturers, therefore, 150 ppm is an FEL, and it is theoretically possible (see below) that 150 ppm could *also* be the LOAEL. The NOAEL, by definition, must be lower than 150 ppm, perhaps substantially so.

Well-accepted and mainstream methods of risk assessment for noncarcinogens (see, e.g., EPA's "Risk Assessment Portal" primer at http://www.epa.gov/risk/dose-response.htm) dictate that if a LOAEL can be estimated in an occupational study, three adjustments to the LOAEL are required to set an RfC or an MRL: (1) adjust from a 40 hr/week occupational exposure to a 168 hr/week continuous exposure—which is to say, divide the LOAEL by a factor of 4.2; (2) divide the resulting number by 10 to try to account for the fact that we want to find a concentration that will *not* cause observable harm (the NOAEL), rather than one that we know does cause harm[5]; and (3) divide again by a factor of 10 to account for the fact that there will be many in the general population who are more susceptible to disease than the average of the small group(s) of workers studied.

So all in all, the RfC in such a case would be the LOAEL divided by approximately 420 (4.2x10x10); in order to move from a level that clearly causes harm in workers to one that is "reasonably likely to cause no harm" in the general population, these adjustments are the necessary way we move "down the dose-response function." Again, the manufacturers and I agree that 150 ppm is definitely a Frank Effect Level: the only question is *how much* lower than 150 ppm the LOAEL is found. The way to give nPB the maximum benefit of the doubt is to (ignore a variety of positive evidence at lower concentrations and…) assume that 150 ppm is both an FEL **and** the LOAEL; that no concentration even slightly lower than 150 ppm would be observed to cause harm in a small worker population. *If* this was the case, then the RfC for nPB would be (150/420), or about 360 ppb. This is somewhat higher than the 40 ppb standard I recommended to the City, but within an order of magnitude of it. Put another way, a general population performance standard of 40 ppb implies that the occupational LOAEL is roughly

---

[5] The large empirical record suggests that a factor of 10 is *probably* sufficient to move downward from a true LOAEL to a NOAEL (see, e.g., S.J. Baird et al. (1996), "Noncancer Risk Assessment: A Probabilistic Alternative to Current Practice," *Human and Ecological Risk Assessment,* **2:** 79-102).

(40x420), or 17 ppm. So the real question the manufacturers' arguments raise is: how likely is it that since 150 ppm is a Frank Effect Level, "149.99… ppm" is a level at which no frank effects would be seen (in other words, 150 ppm is both an FEL and the LOAEL)?

Even if there weren't already various *actual observations* documenting the fact that neurotoxic effects are observed at concentrations well below 150 ppm, at roughly 1-3 ppm (see below), I think it is theoretically unlikely that the dose-response relationship would be so steep, and have a LOAEL so conveniently close to the zone of "criminal dose," that no effects would be observed at or below the 17 ppm concentration that would lead to a performance standard of 40 ppb or below. In effect, all the manufacturers have done is assert that a concentration of roughly 17 ppm *can't* be harmful because 150 ppm clearly *is* harmful, which I believe is not a logical conclusion. If 17 ppm is "safe," it would be because there would be evidence of this, or at least lack of strong evidence against this—and we find neither in the empirical record on nPB (in fact, we find the opposite—evidence of harm well below 150 ppm, and also below 17 ppm).

The illogic of being seriously concerned about 150 ppm and unconcerned about slightly lower exposures is even more pronounced when one considers the carcinogenic effects of nPB. No hypothesis has ever been even suggested, to my knowledge, that there would be a biological threshold for nPB carcinogenicity (this would be unusual, but in the face of persuasive theory and evidence, a few carcinogens are accepted as probably having thresholds). Therefore, the dose-response function must be continuous for some exposures below 62.5 ppm (a clear effect level in female mice) as we try to estimate risk at lower doses. The NTP female mouse lung tumor data is easy to analyze quantitatively, and the response is extraordinarily statistically significant: in my June report, I calculated the (upper-bound)[6] slope of this function to be 1.95×10^{-3} per ppm, which means that the excess cancer risk at 40 ppb is roughly 8 chances in 100,000, not an insignificant risk by any accepted science-policy judgment.

---

[6] Using the upper 95th percentile estimator of the slope here, as EPA does, introduces a trivial amount of "precaution" in this case: the maximum likelihood estimator of the nPB slope factor is 1.34×10^{-3} per ppm.

To summarize the above discussion: observational evidence of harm below 150 ppm is irrelevant to the proposition that the accepted serious danger at 150 ppm implies the need for concern at somewhat lower concentrations (360 ppb or below). Moreover, even if a human (occupational) NOAEL had been demonstrated for nPB below 150 ppm, a margin of safety of at least a factor of 42 (4.2x10) below this concentration would be necessary to protect the general population. But as emphasized in my June 2010 report, we already *have* considerable observational evidence of harm below 150 ppm. The manufacturers have raised some arguments attempting to cast doubt on some of these observations (some of the case series of severe neuropathy, some of the epidemiologic studies of neurological deficits at lower exposures, and some of the rodent cancer bioassay results). However, none of the manufacturers' arguments about the alleged problems with the bioassay or the human studies are convincing. The remainder of this document will discuss some of the problems with these arguments, and will end with a brief note about two new neurotoxicity studies of nPB.

III. Absence of Compelling Rebuttal Evidence:

The overarching problem with the manufacturers' arguments is their incompleteness. For example, it is certainly possible that the Raymond and Ford (2007) cohort had co-exposures to arsenic, which could have accounted for some or all of their neurological damage—but this "finding" would account for only one of three independent and very similar conclusions reached by different groups of researchers studying different worker populations entirely. The "rebuttals" to the Majersik et al. and the CDC conclusions consist only of assertions that ventilation was poor and chemical handling and use was careless in each of the facilities studied, which of course is an argument *for* regulatory controls. Other major concerns I have with the manufacturers' interpretations include:

- <u>(Unrebutted) positive studies trump negative ones</u>. This is not a "thumb on the scale," but rather is the only way to interpret data properly about environmental toxicants, for two different reasons. First, many "negatives" are properly understood as "perhaps zero, but perhaps too small to see"—and

"too small to see" can be quite large depending on how powerful your observations are. Any instrument, measuring tool, or observational study can only detect effects of a certain minimum size. A telescope can reveal large objects invisible through binoculars, which in turn can reveal things undetectable by the naked eye; the objects are always there whether the device can visualize them or not. Similarly, a CT scanner can detect smaller lesions than an ultrasound, which in turn is superior to self-examination. If society cares about an effect of a drug that would harm one out of 10,000 people, it needs to understand that the most likely outcome of testing the drug on 5,000 people is that it will appear to be perfectly safe. These examples do not mean that we should always assume there is invisible and serious danger—only that we should only be as confident as our observations are powerful. Secondly, even "true negatives" (reports of zero effect in which we are confident) may not properly outweigh true positives, when the goal is to avoid needlessly risky alternatives. If the Toyota Camry was the only model of car manufactured, it might be very important to balance the reports of runaway acceleration with the (obviously many more) "reports" of all the tests made on or trips taken in Camrys where the problem *didn't* occur. But Toyota ultimately had to recall vast numbers of Camrys because its owners wanted the (unknown, but clearly non-zero) risk to be reduced, and because buyers had many other alternatives to choose from. I have cited several well-conducted human studies showing irreversible damage from nPB; the 150 (or more, for all I know) studies that might not show these effects (Stelljes White Paper, p. 9) are not of compelling interest to public health professionals trying to gauge the danger.

- Whole-animal (and human) studies trump *in vitro* studies. The further away one gets from studying humans *in vivo,* the less expensive and more ethically palatable the studies become, but they lose power and relevance. As an article provided by the nPB manufacturers correctly states, "Clearly, use of *in vitro* bioassays alone does not provide conclusive evidence regarding potential whole body toxicity in humans" (Hasspieler, Haffner, Stelljes, and Adeli, *Toxicology and Industrial Health,* **22,** p. 312). Accordingly, the fact that human liver cells may allegedly be able to tolerate X ppm of nPB would only be interesting if we didn't already know that actual human beings are harmed by X ppm (or in this case, by roughly X/100 ppm). Moreover, mutagenicity is not necessary for carcinogenicity, and many substances known to damage DNA *in vivo* do not do so in some of the *in vitro* tests referenced in Dr. Stelljes' Powerpoint presentation from October 7, 2010 (slides 4-5). As the later slides acknowledge, nPB is metabolized in the liver, and presumably changed into reactive intermediate(s) that can damage DNA or otherwise initiate tumorigenesis, so it is unclear of what use isolated human liver cells are. These tests do not even *begin* to suggest a coherent theory as to why we might be justified in ignoring the tumors in experimental animals. Note, for example, that the Halogenated Solvents Industry Alliance (the association representing the Perc manufacturers) did advance such a theory, using extensive human *in vitro* results, when OSHA regulated methylene chloride in

1997; OSHA published a very extensive critique, based largely on expert comment from independent scientists, concluding that these experiments were irrelevant and of no consequence (see 62 *Federal Register* pp. 1517-1529, January 10, 1997). The nPB *in vitro* tests are not even as well-developed now as the discredited methylene chloride tests were then.

- Outdated conclusions (offered before definitive new data were generated) need to be discarded, not repeated as if they still apply. The nPB manufacturers cite several recommendations for exposure limits derived circa 2002 (Doull), 2003 (EPA), and 2004 (Stelljes and Wood)—before the three most worrisome neurological studies (Ichihara 2004a; Li et al 2010a; Li et al. 2010b) had been done, before the various case series (Majersik et al. 2007, Raymond and Ford 2007, CDC 2008) had been reported in the literature, and before the NTP cancer bioassay was even begun. These antiquated opinions should carry very little weight in 2010. Similarly, the attachment EnviroTech submitted to the record from Harvey Clewell[7] (Dr. Clewell is a very accomplished mathematical modeler) is irrelevant to our current knowledge of nPB carcinogenicity—it was written in the middle of the 5-year process in which the National Toxicology Program tested nPB in rats and mice, ***before*** the mouse tumor data were available. The fact that years ago, Clewell thought that nPB *might* turn out not to be strongly carcinogenic, *depending* on the results of the pending mouse study, is moot now that the mice did develop an unequivocal and strong lung cancer response.

- EPA has made no statements, scientific or otherwise, suggesting that nPB is less dangerous than Perc. Dr. Stelljes, on behalf of the nPB manufacturers, made two misstatements in his White Paper in the sentence at the top of p. 9: (1) the RfC for Perc is not 0.41 $\mu g/m^3$—it is 16 $\mu g/m^3$ (his error is thus of a factor of 40); and (2) there is no RfC for nPB, draft or otherwise, 1 ppm or otherwise (see Footnote 5 in my Nov. 4 memorandum for an elaboration). More broadly, the nPB manufacturers make much out of the (very outdated) "finding" by the Significant New Alternatives Policy (SNAP) Program at EPA that nPB can be used in the workplace as long as the concentration is below 25 ppm. SNAP is not a regulatory or a public health program—it is tasked solely with recommending *specific* chemicals in *specific* applications (e.g., refrigeration and air conditioning, foam blowing, metal cleaning) when the chemical is less damaging to the ozone layer than prevalent substances in use. SNAP has never looked into dry cleaning, primarily because the primary dry cleaning solvent (Perc) would **also** be promoted under any ozone-friendly environmental policy (neither Perc nor nPB significantly harm the ozone layer). The 25 ppm recommendation from SNAP regarding nPB can only be fairly compared to *no* exposure limit concerns from the same office regarding

[7] "Opinion on the Potential Carcinogenicity of 1-Bromopropane Based on Preliminary Results of the 2008 NTP Rat Bioassay," September 23, 2008, 8 pp.

Perc (that is, 25 ppm is by definition a more stringent limit than no limit at all).[8] It is also very important to understand that these ppm-level recommendations are for **workers,** not the general public—they are useful to compare two substances but not to set levels in the environment. SNAP, in fact, recommends 25 ppm *along with gloves, goggles, and protective clothing* for nPB—surely we don't expect co-located children at a day care center to wear gloves and goggles. (I realize their exposure would be well below ppm levels, but the point is that 25 ppm has nothing to do with Philadelphia's public health regulation). If it is deemed crucial to compare the parallel health-based recommendations of an expert body on the two solvents, the only authoritative such comparison is the ACGIH Threshold Limit Value®, which (at 25 ppm) is 2.5 times higher for Perc than the TLV for nPB (10 ppm)—that is, ACGIH regards nPB as significantly more dangerous at equivalent dose than Perc. Note that ACGIH set the TLV for nPB in 2004, years before many of the new studies on nPB had appeared.

IV. Reaffirmation of the Cancer Conclusions:

- Dr. Stelljes' claim (see pages 7-8 of the White Paper) that the National Toxicology Program does not "officially" regard nPB as a carcinogen is misleading. NTP started this process almost 10 years ago, the bioassay was finished 3-4 years ago, the data were reported last year, and internal and external peer review committees have accepted the findings. In particular, Dr. Stelljes does not mention that the minutes of the November 19, 2009 meeting of the NTP Board of Scientific Counselors were published nearly a year ago, and the BOSC voted unanimously (9-0) to accept the findings of the bioassay report (see http://ntp.niehs.nih.gov/NTP/About_NTP/BSC/TRRS/2009/November/Minutes20091119.pdf). Official representatives of EPA, FDA, NIOSH, and other agencies participated in this review. Contrary to Dr. Stelljes' statement (p. 7), EPA is not "the authoritative body" with respect to carcinogen classification; it is a regulatory agency that participates in, and often defers to, the scientific conclusions of the NTP. It may take the Secretary of HHS months or perhaps even years to "officially" rule on her program's own results, but absent any new data refuting the mouse lung tumor results (and refuting the other compelling but not as statistically significant responses), the NTP will eventually list nPB as "reasonably anticipated to be carcinogenic in humans,"

[8] SNAP acknowledges (see http://www.epa.gov/ozone/fedregstr/59fr13044.html) that when Perc is used as a preferable alternative to ozone-depleting chemicals, it has to be used in accordance with Clean Air Act, Resource Conservation and Recovery Act, and other standards, but these controls are not aimed at indoor concentrations. In any event, the fact remains that SNAP went to some lengths to develop a numerical concentration standard for nPB, but has never seen fit to do so for Perc—so it clearly does not regard nPB as less toxic than Perc.

just as Perc is. This bureaucratic delay should not be used to the detriment of Philadelphia residents.

- The location of the mouse tumors (lung) is not a reason to doubt their relevance to humans. It is not logical to insist that liver tumors should be expected from a compound that is metabolized in the liver. Many, perhaps the majority, of all carcinogens are metabolized in the liver, and yet the sites where animal (and human) tumors are known to occur range from brain to skin to bladder. There is no reason to discount a carcinogen that does not produce liver tumors (indeed, if it *only* produces liver tumors, some scientists and representatives of manufacturers often suggest this is a species-specific effect that *can* be discounted).

- The dosing pattern in the NTP bioassay (chamber air) is completely appropriate. I have not before seen the argument made in Slides 6-7 of Dr. Stelljes' Powerpoint, to the effect that "fur exposure" can cast doubt on inhalation bioassay results. If Dr. Stelljes is suggesting that the nPB should have been instilled directly into the rodent lungs, rather than introduced into the air in their cages, no doubt the manufacturers would have objected to this "unrealistic" design and pointed out that exposed humans would not have nPB instilled into their lungs, but would breathe it in ambient air—just like the actual rodents in the NTP bioassay did. Perhaps skin absorption is important in people too—but if so, that would add to the level of concern, not detract from it.

V. Reaffirmation of the Neurotoxicity Conclusions:

- In a summary of my interpretation of Ichihara et al. 2010a, Dr. Stelljes wrote as follows: "The authors conclude by saying 'there were no severe chronic symptoms suggestive of neurological damage in workers exposed to less than 170 ppm.' This is far different than the inflammatory statement in Finkel (2010) that 1.1 ppm exposure to nPB resulted in complete loss of sensitivity in fingers and toes." His statement is misleading, as the quote actually comes from a subsequent article (Ichihara et al. 2010b), and refers to a different investigation entirely. Ichihara's group certainly did *not* repudiate their own earlier work: 2004a made actual measurements, and 2004b merely interviewed subjects about subjective symptoms related to neurological function (e.g., dizziness, headache), but *no* measurements of nerve conduction velocity, vibration sense, reaction times, visual contrast sensitivity, etc. were sought or obtained. Nothing here casts doubt on the finding in Ichihara 2004a that "One worker showed complete loss of vibration sense on the right toe by tuning fork stimulation. The exposure level for this worker was 1.10 ppm," or on the finding that 14 other workers at higher exposures showed this loss in either fingers, toes, or both. The findings might be explained away by other

evidence (which this White Paper does not provide), but it is not "inflammatory" to quote from a peer-reviewed publication.

- It is certainly possible that some of the case series reports suffered from underestimation of exposure (conditions were actually worse than the investigators realized), but of course much of the manufacturers' arguments about current conditions are that they are *better* than other investigators (NIOSH, Blando et al.) realize.

VI. Brief Update on the 2 New Li et al. Studies:

Both of these 2010 studies (see my Nov. 4 memorandum for full citations) show measurable neurological deficits around 2 ppm—this is very consistent with Ichihara 2004a and supportive of a performance standard at or below 40 ppb:

- The 2010a study involved 86 workers and an equal number of matched controls at three factories in China. The investigators divided the exposed workers into three groups: a "low-exposure group" (median concentration 1.3 ppm), a middle group (median concentration 6.6 ppm), and a high group (median concentration 22.6 ppm). They documented very significant (p values < 0.01) deficits in nerve conduction and vibratory sense in the middle group, and borderline significant deficits (p values of 0.06 and 0.02) in the low-exposure group.

- The 2010b study (abstract only in English; full text in Chinese) looked only at female workers, and documented very similar deficits (with the addition of altered behaviors including confusion and anxiety) at a median concentration of 2.8 ppm nPB.

VII. Conclusions:

One complete set of cancer bioassays has been conducted by the NTP for both Perc and nPB; at similar concentrations commonly found in workplaces (50 ppm for Perc; 62.5 ppm for nPB), nPB caused many more excess tumors than Perc did. Both of

these findings are very worrisome in light of current occupational exposures in the "high dose" range (federal, state, and local regulatory agencies typically strive to reduce ambient concentrations of carcinogens to levels thousands of times lower than those we can observe to cause significant tumor increases in only 50 animals)—but the nPB bioassay is more worrisome than the Perc bioassay, because the control rate of lung tumors (nPB) is so much lower than the control rate of mononuclear cell leukemias (Perc). No theory has even been advanced that would begin to explain the nPB female mouse lung tumors (or the female rat intestinal tumors, for that matter) as irrelevant to humans or in any other way artifactual. Therefore, we must regard the bioassay results as supporting strict controls on each of the two solvents.

nPB shows a constellation of irreversible clinical neuropathic effects at roughly 100-200 ppm, and likely at somewhat lower concentrations, in several well-conducted studies; Perc shows no such syndrome at comparable levels. Although it is possible that one of the case series may have been confounded by arsenic exposure, the other two series involve a significant number of cases, and the only comment the manufacturers have on these studies is that the concentrations the affected workers were exposed to *may* have been closer to 100-200 ppm than to 50-100 ppm. That, of course, does not change the finding; moreover, the observation that "additional cases [of irreversible neuropathy] should occur only if operators do not follow recommendations for safe operation" (Stelljes White Paper, p. 5) is, obviously, an argument in *favor* of the City's efforts to ensure that nPB is used safely.

At much lower concentrations (1-3 ppm), nPB exposure has documented effects on nerve conduction velocity and vibratory sense. Two of the three studies documenting this same finding (Li et al. 2010a and 2010b) are newly-published, but no doubt has (as yet) been cast on these findings; Ichihara et al. 2004a is unrebutted by the manufacturers, other than their quoting a sentence from Ichihara 2004b that is irrelevant to the earlier study.

Our knowledge of the quantitative potency of nPB (and of Perc) will continue to increase as new data become available, but at the present time, I remain convinced that it

would be extremely inappropriate scientifically not to subject nPB to at least the same stringency of control as the City has determined to be appropriate for Perc.