

SUPPLEMENTAL REPORT TO THE CITY OF PHILADELPHIA  
DEPARTMENT OF PUBLIC HEALTH/ AIR MANAGEMENT SERVICES

INCREASED TOXICITY and CARCINOGENICITY OF  
*n*-PROPYL BROMIDE (1-BROMOPROPANE)  
RELATIVE TO PERCHLOROETHYLENE

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## 1. INTRODUCTION:

The city of Philadelphia has proposed to accelerate the federal (EPA) phase-down of perchloroethylene (“Perc”) in dry cleaning, due to health concerns for the residents (especially children) and workers in establishments co-located with cleaners. Although some co-commercial cleaners will likely stay with Perc and control exposures in co-located workplaces to the performance standard established in the new regulations (at or below 40 ppb), others will switch to different solvents, and all cleaners with co-located residences or “sensitive” facilities (schools, day care centers, hospitals, etc.) will either have to switch to another solvent or change their service to “drop mode” (for cleaning at another location). The Ad Hoc Subcommittee of the Air Pollution Control Board (APCB) was concerned about ensuring that alternative solvents whose use might increase on account of the regulations would be safer whenever possible, and certainly not more toxic than Perc: as its February 16, 2010 memo to the full APCB indicated, the Subcommittee wanted Air Management Services to “Promote switching to clearly safer substitutes and seek to prevent the use of other hazardous toxic substances as a substitute” (for Perc). Of the various “drain and drop” and other alternatives to Perc, some are clearly safer (e.g., wet cleaning, supercritical CO<sub>2</sub>,) some are probably less toxic but may raise concerns about flammability, but some are clearly more toxic.

I was asked by AMS to summarize the current scientific information about the relative toxicity of Perc and one particular alternative—*n*-propyl bromide (“nPB,” also known as 1-bromopropane). This report also discusses more generally the risk management issues that arise when a regulatory agency is faced with the likelihood that well-meaning controls on a particular substance will lead to a net increase in harm (Finkel 2007).

Absent a more comprehensive regulatory structure, the obvious risk-increasing response to controls on Perc in dry cleaning will be for some cleaners to substitute nPB for Perc. nPB was relatively unknown in the U.S. 10 years ago, but since then has been aggressively marketed as an unregulated alternative first to methylene chloride (regulated by OSHA in 1997), and later to Perc following EPA’s announced phase-down in dry cleaning. For example, here is a very frank description from an industry website:

<http://www.textilecleaning.com/npropylb.htm>. DrySolv is a newer alternative solvent that is available for drycleaners to **get out from under perc and its related rules, regulations, taxes, continually rising cost and general bad publicity.** (emphasis added)

One of the major remaining manufacturers of nPB describes its advantages thus:

<http://www.envirotechint.com/products/dry-cleaning/details/drysolv>. **DrySolv** is a patented dry cleaning solvent that is non-chlorinated, non-flammable, non-hazardous, and is vastly more environmentally responsible than PERC. It is a direct replacement for PERC and other cleaning chemicals in the dry cleaning industry that works in your existing PERC dry cleaning machine. Research has shown **DrySolv** to be superior

to PERC in that it cleans better, and cleans faster. Because **DrySolv** is non-hazardous, costly issues such as environmental compliance and waste disposal of PERC are eliminated or significantly reduced.

As this report will summarize, *in my expert opinion, far from being “non hazardous,” nPB is a potent neurotoxin, and has recently been shown to be a potent animal carcinogen.* To a reasonable degree of scientific certainty, equal exposures to nPB will harm more residents and workers than would exposures to Perc: both are harmful substances, but nPB is the more harmful of the two.

Even worse than comparable levels of exposure to the two solvents (in theory) would be the potential for much *greater* exposures to nPB than to Perc in actual practice. nPB is more volatile than Perc (its vapor pressure is approximately 111 mm Hg at 25 C, whereas the vapor pressure of Perc is about 18.5 mm Hg), and so with equivalent equipment and controls, cleaners who use nPB would be expected to experience higher concentrations than if they used Perc. Indeed, data from a forthcoming journal article (Blando et al., 2010) shows that in four New Jersey dry cleaners who recently switched from Perc to nPB, air concentrations of nPB were as high as 54 ppm as an eight-hour time-weighted average—Perc concentrations using similar (“third-generation”) equipment as the shops in New Jersey use tend to be only in the range of 1-5 ppm (OSHA 2006). Moreover, a regulation that only mentioned Perc would further tilt the playing field towards greater exposures to substitute materials, because the actual comparison would be of controlled exposures to Perc versus uncontrolled exposures to the substitute(s). Data from AMS (referenced in Section 5 of my January 2010 final report on Perc) shows that uncontrolled exposures to Perc in co-located facilities can approach 1 ppm (a reading of 864 ppb was documented with limited sampling); although interventions to control Perc emissions can reduce these concentrations to the 40 ppb performance standard or below, there would be no requirement or incentive for cleaners to undertake control measures if they were permitted to switch to nPB without such restrictions. So although this report will summarize the risk-increasing problem of comparable exposures to nPB versus Perc, in reality the untoward consequences of a regulation that does not anticipate and address adverse substitution would be much greater.

## 2. SCIENTIFIC OVERVIEW:

As this report will summarize, Perc at high levels (approx. 100 ppm) can cause moderate neurologic symptoms in exposed humans; at low levels (1 ppm and below) it can cause much less severe but still worrisome neurobehavioral symptoms. On the other hand, at high levels (roughly 50 ppm), nPB can cause *severe* neurological damage, but there are as yet no studies of neurobehavioral effects (present or absent) of nPB at low levels. Absence of evidence is not necessarily evidence of absence: in other words, we can't assume that nPB won't cause the same (or worse) neurobehavioral effects as Perc does at low levels. But presence of evidence trumps absence: in other words, we can be fairly

confident that there is *not* a “Perc syndrome” of irreversible neuropathy at roughly 50-100 ppm, because we have tested Perc at these levels and found different (less severe) human effects.

Moreover, we can now compare the carcinogenic potency of the two solvents directly. The National Toxicology Program has now finished a set of lifetime cancer bioassays of nPB (NTP, 2009) to complement its 1986 studies of Perc. nPB is **clearly** somewhat more potent a carcinogen than Perc (see Section 2-C below). Although absence of evidence is not definitive here, I note that there are various interesting (though, in my opinion, not currently fully developed) theories as to why some of the Perc cancer results may be partially or wholly irrelevant to humans (see pp. 12-17 of my January 2010 report)—there have been no such mechanistic attempts to explain away the variety of tumors found in the nPB bioassays.<sup>1</sup>

Bitter experience with human diseases caused by low-molecular-weight brominated compounds (e.g., male sterility in Dow chemical plant workers caused by dibromochloropropane (“DBCP”), a compound closely related to nPB; neurological disease in workers exposed to the pesticide methyl bromide) suggests that brominated compounds are generally more toxic to humans than their chlorinated analogs. Several of these brominated compounds have since been banned nationally and internationally. This pattern of toxicity is consistent with the fact that the carbon-bromine bond is weaker than the C-Cl bond, and thus a brominated compound may more readily form an electrophilic intermediate that reacts with DNA, as compared to its chlorinated analog. Table 1 shows four pairs of compounds that differ only with respect to whether they contain bromine or chlorine atoms, showing that the brominated analog is up to 33 times more potent<sup>2</sup>:

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<sup>1</sup> Note particularly that in the Perc bioassay, 22 percent of the test animals developed the sentinel tumor type (mononuclear cell leukemia) with NO exposure, whereas in the nPB bioassay the control rate (of lung tumors) was only 2 percent. Although I believe the MCL response for Perc is real and reliable (see my January 2010 report), the enormous increase in lung tumors above control rates with nPB is even more compelling.

<sup>2</sup> Note that although Perc is, of course, a chlorinated hydrocarbon, it does not appear in this table because there is essentially no toxicological or use information on “tetrabromoethylene,” which would be its direct brominated analog.

TABLE 1			
DIRECT COMPARISON OF POTENCIES OF BROMINATED v. CHLORINATED ANALOGS			
Note: when comparing RfCs, the more potent toxicant is the one that has the <b>lower</b> value (a lower concentration corresponding to the same “likely to be without appreciable risk” outcome); when comparing cancer potency factors (“q <sub>1</sub> ” values), the more potent carcinogen has the <b>higher</b> value (more tumorigenicity per unit of exposure).			
Substance	Brominated Analog	Chlorinated Analog	Ratio Br:Cl toxicity
Ethylene di...X	Ethylene dibromide: q <sub>1</sub> * = 6x10 <sup>-4</sup> (per ug/m <sup>3</sup> )	Ethylene dichloride: q <sub>1</sub> * = 2.6x10 <sup>-5</sup> (per ug/m <sup>3</sup> )	23 : 1
Methyl X	Methyl bromide: RfC= 5x10 <sup>-3</sup> mg/m <sup>3</sup>	Methyl chloride: RfC= 9x10 <sup>-2</sup> mg/m <sup>3</sup>	18 : 1
Vinyl X	Vinyl bromide: RfC=3x10 <sup>-3</sup> mg/m <sup>3</sup>	Vinyl chloride: RfC=1x10 <sup>-1</sup> mg/m <sup>3</sup>	33 : 1
Chloro-di(X,X) propane	Dibromochloropropane (“DBCP”): RfC= 2x10 <sup>-4</sup>	1,2,3-trichloropropane: RfC=3x10 <sup>-4</sup>	1.5 : 1

It is also important to note that various federal, state, and international expert bodies are gradually developing recommended or mandatory exposure limits for nPB that are stricter than the corresponding ones for Perc (Table 2). Each of these expert bodies develops recommended or binding exposure limits based on a careful analysis of all available toxicologic and epidemiologic data, applying a coherent set of assumptions and rules for interpreting such data. Note in particular that these lower limits for nPB were all set *before* the late 2009 release of the National Toxicology Program’s lifetime cancer bioassay on nPB, which if incorporated would tend to drive the recommended limit lower for nPB.

TABLE 2			
NATIONAL AND INTERNATIONAL EXPOSURE LIMITS FOR nPB and PERC			
Type of Limit	Limit for Perc	Limit for nPB	Ratio Perc : nPB
ACGIH Threshold Limit Value®	25 ppm	10 ppm	2.5 : 1
California OSHA PEL	25 ppm	5 ppm	5 : 1
Worksafe British Columbia PEL	25 ppm	10 ppm	2.5 : 1

In addition to these decisions by expert bodies, individual companies have made decisions about nPB; in particular (Murphy 2001), a major multinational chemical company decided almost 10 years ago (long before the case reports of neurotoxicity and the cancer bioassay were available) that it would cease marketing nPB for solvent applications due to its toxicity. The document announcing that decision said in relevant part:

“nPB is a part of a toxicologically suspect family in which several compounds have toxic properties identified in animals and confirmed in humans. In 1995 and then in 1996, we learned that isopropyl bromide, the structural isomer of nPB, had caused serious reproductive function problems in Korean and then in Chinese workers as well as blood effects following its use as a degreasing solvent... As the effects observed in animals for iPB have also been demonstrated in humans when used as solvent, the concerns expressed in 1997 about the potential effects of nPB in solvent applications are reinforced.”

In addition, at least two other manufacturers have limited or eliminated the production of 1-BP for solvent applications. Great Lakes Chemical no longer sells 1-BP solvent blends. Albemarle Corp. has stated that use of 1-BP in adhesive and other applications in which 1-BP exposure cannot be controlled should be restricted or prohibited (NTP, 2003).

### 3. DETAILED TOXICOLOGICAL COMPARISON

The LC<sub>50</sub> (the airborne concentration that kills ½ of all treated animals) for nPB is approximately 7,100 mg/m<sup>3</sup>; the LC<sub>50</sub> for Perc is approximately 35,000 mg/m<sup>3</sup>, suggesting that nPB is roughly 5 times more acutely toxic than Perc. However, more relevant to regulatory policy are comparisons of chronic exposures to lower levels of the two substances.

#### A. Neurotoxicity:

nPB, like Perc, can damage the central and peripheral nervous systems, but evidence to date strongly suggests that nPB is the more potent neurotoxin of the two. The severe effects of weakness and spasticity of the leg muscles in humans correspond closely to effects seen in laboratory animals exposed to nPB:

- Ichihara et al. (2004) studied 27 female workers in an nPB production factory who were exposed to an average of 3 ppm (range 0.3 to 49 ppm). 15 of the workers showed diminution of the ability to sense vibration in the fingers and toes, including one worker (who lost this ability completely) whose exposure was 1.1 ppm.
- Majersik et al. (2007) studied six workers who used a solvent containing 70% nPB to glue together foam pieces; their exposures ranged from 91 to 176 ppm,

with durations of between 3 to 36 months. The workers experienced weakness and spasticity of the legs, chronic pain, memory loss, urinary incontinence, and daily headache while working with nPB. Even two years after cessation of exposure, some of the workers suffered from “markedly impaired cognitive function.”

- Raymond and Ford (2007) studied eight workers exposed to nPB in glue used in a furniture factory in North Carolina. Average exposures were approximately 80 ppm. The workers developed unsteady, spastic gaits, loss of balance, and other neuromuscular signs and symptoms—in at least two of them, adverse effects (albeit milder in severity) were persisting eight years after having changed employment and presumed cessation of exposure.
- The CDC (2008) reported on two workers with severe nPB neurotoxicity: (1) an electronics worker in Pennsylvania exposed to roughly 180 ppm developed ataxia (difficulty walking), which was persisting more than a year after cessation of exposure; and (2) a dry cleaner in New Jersey who used “DrySolv” (see above) developed tingling, numbness, muscular twitching, and visual disturbances—no information was presented as to whether these symptoms persisted after he began using a respirator at work (obviously, co-located residents and workers would/should not have the option of using protective equipment...). CDC wrote that this case “*likely represents a sentinel case of neurologic toxicity in the dry cleaning industry, and additional cases could occur as dry cleaners switch from perchloroethylene use to 1-BP.*”

Although Perc clearly can cause dizziness and CNS depression at very high levels (above 100 ppm), at levels comparable to those in these nPB case reports and studies, *nothing like the “nPB syndrome” of gait disturbances and pain has been seen with Perc*, over many decades of use. For example, although some of the earlier studies EPA references (Lauwerys et al. 1983; Seeber 1989—see p. 4-54 of EPA 2008) document effects of Perc at roughly 20 ppm that are more severe than the neurobehavioral effects used to set the RfC (e.g., lightheadedness), these studies revealed “no fine motor function deficits”—whereas slightly higher levels of nPB have caused irreversible effects on the *gross* motor function of exposed workers.

In summary, at comparable levels (roughly 50-100 ppm), Perc produces moderate neurotoxic effects (diminished sensitivity to vibration; reduced nerve conduction velocities), but nPB can produce severe and apparently irreversible neuropathy, affecting gait and cognition. The neurobehavioral effects of Perc at much lower levels (1 ppm and less), such as decreased reaction time and decreased color vision sensitivity, have not been looked for (yet) with nPB—but whether or not they are shown to occur, the clear danger of nPB at higher exposures makes controlling nPB levels an important addition to the Philadelphia regulation governing the use of Perc in co-located dry cleaners.

## B. Reproductive Toxicity:

There is much more concern about nPB than about Perc along this dimension. In particular, most of the workforce (64 percent of the females and 75 percent of the males) of an entire factory in Korea was sterilized due to exposure to roughly 12 ppm of 2-BP (isopropyl bromide).<sup>3</sup> 2-BP is a different substance than nPB, but its very high toxicity is relevant here because it is an inevitable contaminant of the commercial manufacture of nPB.<sup>4</sup> California has listed nPB as “known to cause developmental toxicity in both females and males” since 2004—it does not list Perc as a developmental toxicant.

The NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) evaluated the potential for 1-bromopropane (nPB) to produce adverse reproductive and developmental effects in humans (NTP, 2003). CERHR concluded that there was convincing evidence for reproductive and developmental toxicity in experimental animals. Evidence in humans was limited, but in the monograph, note was made of a new case that was not available to the expert panel indicating positive findings in women (altered menstruation) occupationally exposed to 1-bromopropane. The overall NTP conclusion was that “there is serious concern for reproductive and developmental effects of 1-bromopropane at the upper end of the human occupational exposure range (18 to 381 ppm).” *“Serious concern” is the highest level of NTP conclusion regarding the possibilities that human development and reproduction might be adversely affected.*

## C. Carcinogenicity:

The U.S. National Toxicology Program began testing nPB in roughly 2001, and released an extensive report (NTP 2009) in late 2009. As with other brominated alkanes of low molecular weight tested previously, nPB showed “clear evidence” (according to NTP) of carcinogenicity in multiple animal bioassays. NTP noted that nPB caused rare tumors of the large intestine in both male and female F344 rats, and tumors of the lung and

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<sup>3</sup> Note especially that the workers in the North Carolina furniture factory (Raymond and Ford 2007) were found to have been exposed to 2-BP at levels up to 0.68 ppm—this is less than 1/10 the amount that caused severe reproductive toxicity in Korea, but it shows that commercial formulations containing nPB in the U.S. may well have significant trace amounts of 2-BP. It makes sense that 2-BP levels would be about 1/200 that of 1-BP in air, since (Shubkin and Liimatta 1998) one of the patent holders recommends that when producing nPB, “the isopropyl bromide content should be kept low—for example, within the range of from about 0.01 to 0.5 %.” The higher figure (0.5%) corresponds to 1 part in 200.

<sup>4</sup> Note that because of trade secret concerns, we also don’t know much about the stabilizers added to nPB. Apparently, while commercial Perc formulations used in dry cleaning only require about 1% stabilizer content, nPB products require about 6-7%. Although depending on the identities of the stabilizers, this may not be a public health issue, even with stabilizers added nPB is more corrosive to metal than Perc, and thus may be harder on dry cleaning equipment (see, e.g., the IRTA 2009 article which interviews a dry cleaner in California who claims that switching to nPB created a cloud of acid that “ate a hole in his boiler, completely destroyed the PERC machine and also corroded a laundry dryer in the facility beyond repair”).

bronchus of female mice—it also noted that tumors of the skin, pleura (mesothelioma), and pancreas in rats may have been related to nPB exposure.

EPA has not yet analyzed the nPB bioassay data to calculate a cancer potency factor (CPF) that could be compared to the CPF for Perc. As described in detail in my January 2010 report, the EPA CPF for Perc underwent an extensive set of modifications to account for the different pharmacokinetics of absorption, partition, and excretion in rodents versus humans—no such adjustment can be made for nPB because no PBPK model currently exists for that compound. Nevertheless, it is routine and instructive to compare the CPFs on an equal footing (that is, with no PBPK modifications). I estimated the dose-response curves for both substances using a computer program (“MSTAGE87,” courtesy Edmund Crouch, Ph.D.) that emulates EPA’s linearized multistage program, and then, following EPA practice, calculated the upper 95<sup>th</sup> percentile confidence limit on the linear term of the dose-response function, which EPA terms “ $q_1^*$ ,” or the CPF.

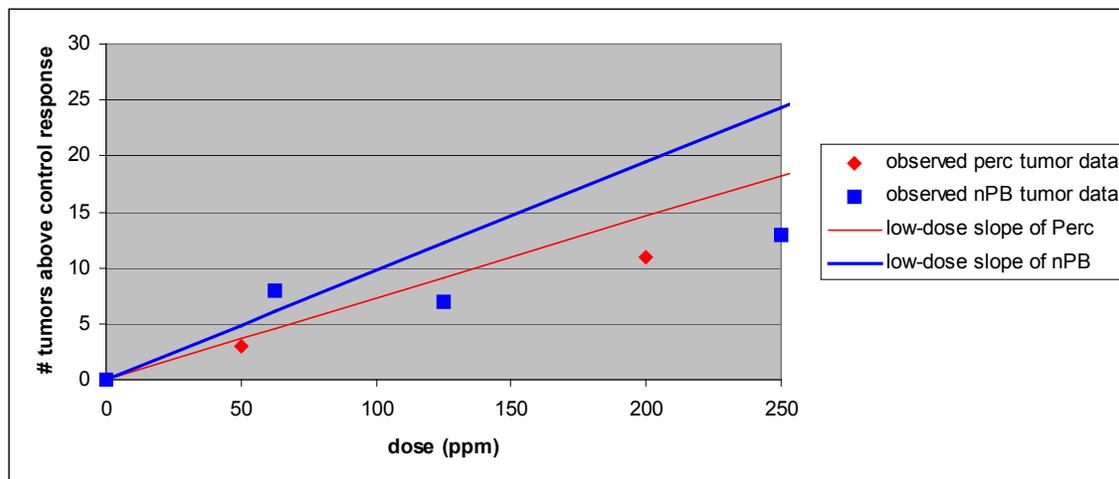
The most sensitive sex/strain/site combination for Perc carcinogenesis appears to be the mononuclear cell leukemia response in male rats (see January report). In that experiment, Perc caused 14 cancers at 50 ppm (all Perc and nPB results are out of 50 animals per dose group), 22 at 200 ppm, and 27 at 600 ppm—at no exposure (control group), 11 cases of MCL were noted. In the recent bioassay of nPB, there was 1 lung/bronchus tumor at no exposure, 9 at 62.5 ppm, 8 at 125 ppm, and 14 at 250 ppm. ***Note that nPB clearly caused many more excess tumors at lower doses as compared to Perc.***

The dose-response software yielded a  $q_1^*$  value of  $1.95 \times 10^{-3}$  (per ppm) for nPB, as compared to a value of  $1.46 \times 10^{-3}$  for Perc. By this comparison (which, again, cannot take PBPK into account, which could result in higher or lower relative potency for nPB compared to Perc), ***nPB is roughly 34% more potent per unit of exposure a carcinogen than Perc is.***<sup>5</sup>

The chart below shows the two bioassays (in the black-and-white version of this document, the Perc data points are diamond-shaped and the nPB data points are squares; the upper-bound linear slope estimate is a thicker line for nPB and a thinner line for Perc). In both cases, the y-values represent the number of tumor-bearing animals *above* the number in the control group. Note that the upper confidence limit on the low-dose slope is larger (steeper) for nPB than it is for Perc.

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<sup>5</sup> Note that the recent National Academy of Sciences committee (NAS 2010) that looked carefully at the carcinogenicity data for Perc was divided about the confidence with which we should rely on the rat leukemia response, because of a possible species-specific mechanism of action. Although I agree with those on the NAS committee who regard the leukemia data as relevant, if one did compute Perc’s cancer potency based on the kidney tumor data, the  $q_1^*$  value would instead be  $3.8 \times 10^{-4}$ , which would make nPB more than *five times* more potent a carcinogen than Perc.



#### 4. POLICY OVERVIEW:

Risk-risk tradeoffs are real and compelling—although sometimes there is too much uncertainty about the eventual behavioral response to regulation (Finkel 2007) for government to regard a purported tradeoff as legitimate, there clearly are cases where as one substance is more tightly controlled, a more toxic substitute will almost certainly replace it, causing a net increase rather than a decrease in risk. This reflects lack of good planning by government; the “regulatory czars” under both the Bush and Obama administrations (Sunstein, 1996; Graham and Wiener 1995) have each written extensively about the need for statutory change so that agencies will be forced to consider the risk-increasing consequences of their regulations.

There are three basic responses to a valid concern that regulating X will cause substance Y to be used, with net risk-increasing results: (1) regulate X and ignore the consequences; (2) forego regulating X entirely; or (3) regulate both X and Y. The first response is dereliction of duty, and the second is cringing in the face of a more complicated problem; the third course of action generally makes the most sense.

Examples already exist of federal and state agencies causing increased net risk by regulating particular solvents without considering that users will seek unregulated substitutes, especially whenever one solvent can be “dropped in” to replace another with little or no retrofitting. For example, California cracked down on Perc use as a brake-cleaning solvent in auto repair shops in the late 1990s; since then, case reports have arisen (CDC 2001) connecting serious neurological damage in auto repair workers whose shops switched to *n*-hexane.

The momentum is clear that regulatory agencies should and will think more seriously about risk-risk tradeoffs. It is of course best to do so before it is too late. After the

“genie is out of the bottle,” irreversible harm to human health or the environment may have occurred, but it is also important to emphasize that irreversible *expense* may also have been incurred: dry cleaners deserve the regulatory agency’s best current judgment about which substance(s) should not be used as substitutes *before* they are led to make investments that later prove unwise. Sometimes the risks of current materials and their substitutes confront society with a true dilemma—but this is *not* such a case—there are ways to clean clothes safely without using a solvent that is even more toxic than Perc.

## 5. CONCLUSIONS

nPB is a potent neurotoxin, and has recently been shown to be a potent animal carcinogen. As a result of my scientific analysis, I recommend that Philadelphia add a provision to its draft regulation forbidding dry cleaners to substitute the more toxic alternative nPB for perchloroethylene (“Perc”). This is a laudable and forward-thinking improvement to the federal (EPA) dry cleaning rule, which will, in my opinion, increase risks to workers and nearby residents by encouraging the substitution of the (federally) unregulated nPB for Perc in locales other than Philadelphia.<sup>6</sup> To a reasonable degree of scientific certainty, exposures to nPB will harm more residents and workers than would exposures to Perc: both are harmful substances, with nPB the more harmful of the two. In addition to its plans to provide outreach and education to dry cleaners about ways to meet or go beyond the 40 ppb performance standard in co-commercial facilities that wish to continue to use Perc, I applaud the City’s intention to provide informational materials about the benefits of less toxic substitutes for Perc in dry cleaning.

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<sup>6</sup> Note that in the substitution of hexane for Perc, one could reasonably argue that while both substances are neurotoxic, only Perc is a probable carcinogen, and so the tradeoff was not necessarily an unfavorable one for workers. As this report will summarize, however, both Perc and nPB are animal carcinogens, and so no such “silver lining” can be invoked in this case. Switching to nPB is likely to increase both cancer and non-cancer risks.

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