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Dr. Lori White
Designated Federal Officer for the BSC
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Dear Dr. White,

The following comments are submitted on behalf of the more than two million members and supporters of People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM) in response to the nominations of substances to NTP for study in 2010 (October 19, 2010; Federal Register 75(201): 64311). Our organizations are committed to using the best available science to both protect animals from suffering and to promote the acceptance of human-relevant methods for risk assessment.

Specific comments are submitted on cholesterol and lipid modulating agents, N-butylbenzenesulfonamide and selected flame retardants. NTP has recommended additional animal tests for these substances that would result in the poisoning and death of thousands of animals if carried out. In each case, we urge NTP to thoroughly consider human experience, existing toxicity data and the application of non-animal test methods in order to avoid irrelevant and duplicative animal tests.

Thank you for your attention to these comments. I can be reached at (757) 622-7382, ext. 8001, or by e-mail at josephm@peta.org.

Sincerely,

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Cholesterol and Lipid Modulating Agents: Toxicological Approaches to Assessing Complex Mixtures

Two nominations, both apparently by the same anonymous private citizen, are presented as one Research Concept addressing the cumulative toxicity of mixtures with regard to cholesterol and lipid modulating agents. Developmental endpoints will be evaluated following *in utero* exposure, presumably of rats, although this is mentioned only indirectly – "the assessment of developmental effects in the rat can be undertaken readily in the short term." Specific developmental endpoints are not identified, except for cardiopathic effects in fetal rats produced by dichloroacetic acid (DCA), a common disinfection byproduct, when administered at high doses. While myopathies are identified as one of the major adverse effects of the statin class of cholesterol-lowering drugs in animals, the cited reference (Hrab et al., 1994) reports these effects of fluvastatin as maternal.

Modes and Mechanisms of Action

The Research Concept asserts that "… the development of approaches to predict the toxicological outcomes of exposure to mixtures, be it from chemicals with similar modes of action or similar adverse outcomes, is necessary." Also, a key issue to be addressed is that while "[r]ecent studies have found that chemicals that target the same signaling pathway or tissue elicit dose additive toxicity regardless of their specific mechanisms of action…, further studies are necessary to determine if this is true for other modes of action." Therefore, it is unclear from the beginning whether similar modes of action are to be included or excluded from the scope of the proposed research.

It is also unclear how mechanisms of action involving peroxisome proliferator activated receptor (PPAR) agonism are hypothesized to be involved. The National Academy of Sciences (NAS) report, *Phthalate and Cumulative Risk Assessment: The Task Ahead*, a principle reference for the Research Concept, emphasizes that although it recommends focusing on common adverse outcomes in cumulative risk assessment, information on mechanisms of action is still useful – in part for determining the relevance of effects observed in animals to humans. The Research Concept notes that the fibrate class of cholesterol-lowering drugs are PPARα agonists and that interaction with these receptors is an activity shared by a number of environmental chemicals, including phthalates, perfluoroalkyl sulfonates and carboxylates (PFAAs), and the water contaminants trichloroethylene (TCE) and trichloroacetic acid.

However, a 2005 review by Peraza et al., cited in the Research Concept, concludes that while phthalates, PFAAs, and TCE are relatively weak PPARα agonists and can cause developmental toxicity in animals, ligand activation of PPARα is not likely a general mechanism of action leading to developmental toxicity. In addition, since administration of fibrates during pregnancy does not result in overt teratogenesis (in humans or animals, see below) while exposure to the relatively weak PPARα ligands does, this argues against the hypothesis that activation of PPARα during development is a central mechanism of action leading to teratogenesis. Peraza et al. cite Peters et al., 1997, who show that administration of the phthalate DEHP during organogenesis causes neural tube defects in both wild-type and PPARα -null mice, demonstrating that PPARα is not required to mediate this effect, and offer the alternative hypothesis that the developmental and/or reproductive effects induced by phthalate exposure may instead result from a zinc deficiency.

Chemical Selection

The NAS report concludes that the selection of chemicals to include in a cumulative risk assessment will depend on whether there is potential for exposure in which the chemicals would exhibit common adverse outcomes. However, as noted above, specific developmental endpoints are not identified in the Research Concept, with the exception of cardiopathic effects for DCA at higher doses. Clearly, cumulative effects must be identified before they can be assessed. In particular, there is no discussion of which, if any, of the reproductive tract abnormalities constituting the phthalate or androgen insufficiency syndromes will be evaluated. The NAS report defines the phthalate syndrome in considerable detail. It includes "underdeveloped or absent reproductive organs, malformed external genitalia (hypospadias), undescended testes (cryptorchidism), decreased anogenital distance, retained nipples, decreased sperm production, and regions of Leydig cell hyperplasia." The report suggests that other agents that can produce "androgen insufficiency" in the developing fetus might produce effects on male reproductive development that would include many of the same malformations.

Human Relevance

As noted above, the Research Concept states that fibrates, phthalates, haloacetic acids, and PFAAs have been implicated as developmental toxicants. In particular, the discussion of toxicity focuses on fibrates and statins, phthalates, and DCA. For each of these, the relevance to human exposures of developmental toxicity observed in animals is questionable.

Peraza et al. (2005) concludes that there is no strong evidence that fibrates, specifically clofibrate and gemfibrozil can cause developmental toxicity even in animals, although clofibrate can cause some signs of maternal toxicity at doses considerably higher than those used therapeutically (>500 mg/kg).The Research Concept notes that statins are contraindicated in pregnancy and cites prescribing information for fluvastatin in which it is noted that while there are no data with fluvastatin in pregnant women, rare reports of congenital anomalies have been received following intrauterine exposure to other 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. An uncontrolled case series reported by Edison and Muenke (2004) which found adverse developmental outcomes in women following exposure to cerivastatin, simvastatin, lovastatin, or atorvastatin is also cited. While DCA produces cardiopathic effects in fetal rats, apparently by inhibiting HMG-CoA reductase activity, these effects are observed only only at very high doses (900-2,400 mg/kg; Epstein et al., 1992). While no data on environmental levels of DCA are cited, as a disinfection by-product, human exposures might reasonably be expected to be far lower and therefore of questionable relevance even as part of a cumulative risk assessment. As noted above, myopathies produced by fluvastaitin in animals are maternal (Hrab et al., 1994).

The NAS report frequently raises questions regarding the human relevance of developmental toxicity produced by phthalates in animals. It notes that few human data on the health effects of phthalate exposure are available; instead, most are from laboratory studies of rats, which have been shown to be the most phthalate-sensitive of the species tested. Also, while it cites two reports of an association between phthalate exposure and reduction in semen quality in humans, it notes that the human studies did not find this reduction to be associated with mono-2-ethylhexyl phthalate (MEHP), which is inconsistent with the animal data. Four "small studies" linking maternal exposure to specific phthalate metabolites with adverse outcomes in the children are cited; however, while positive correlations between DEP exposure and effects have been noted in human studies, DEP exposure does not cause phthalate syndrome effects in animals. The report suggests that the positive findings on DEP in humans may in part reflect differences between

rodent and human toxicity. While not cited in the NAS report, it is worth noting that Rais-Bahrami et al. (2004) found no developmental effects for di(2-ethylhexyl) phthalate (DEHP) in adolescents who had been exposed to high medical treatment-related levels as neonates.

With regard to data gaps, the NAS report identifies initiatives to answer questions concerning human exposure as research needs that would greatly refine any cumulative risk assessment of phthalates exposure assessment in humans. It also includes epidemiologic studies to evaluate potential health outcomes of phthalate-antiandrogen exposures and assess the cumulative effects of phthalates and other antiandrogens among the initiatives it outlines for toxicity assessment.

***In Vitro* Approaches**

Although not discussed in the Research Concept, the NAS report and other references offer numerous examples of the application of non-animal approaches to cumulative risk assessment.

The NAS report cautions that "[t]he uncertainties and knowledge gaps call for appropriately conservative approaches that incorporate default assumptions about the likely number of antiandrogens that might contribute to human exposure scenarios." The committee proposes beginning with a screening step in which a mathematical model incorporating estimated values for human exposures and tolerable daily exposures as well as assumptions about the potency and prevalence of unknown antiandrogens is used to identify scenarios in which the cumulative risks posed by phthalates and related chemicals can be safely regarded as low.

With regard to the identification of antiandrogens that might contribute to disrupting male sexual differentiation, the NAS report cites the screening efforts of Kojima et al. (2004) and Vinggaard et al. (2008) using *in vitro* reporter gene assays as well as the development of a quantitative structure-activity relationship (QSAR) model for AR antagonizing potential (Vinggaard et al., 2008). In addition, this laboratory used a similar reporter gene assay to study the mixture effects of five dissimilarly acting pesticides *in vitro* (Birkhoj et al., 2004).

Finally, effects on HMG-CoA reductase activity of DCA, statins, other agents, and metabolites are particularly well suited to *in vitro* approaches using cultured hepatocytes or purified enzyme (Stacpoole, 1983).

Conclusions

The Research Concept presented fails to articulate the hypotheses to be tested, including which chemicals – representing the same or different mechanisms of action and/or adverse outcomes – will be tested. It also fails to identify the specific developmental endpoints to be assessed. It is unclear as to whether similar modes of action are to be included or excluded from the scope of the proposed research. It is also unclear as to what role the PPAR agonism of several of the chemicals discussed is suspected to play. The relevance to human exposures is questionable for all of the chemicals discussed and there is even serious doubt expressed in the cited literature as to whether fibrates can cause developmental toxicity in animals. Although a variety of non-animal approaches are clearly suitable to a preliminary investigation, none are mentioned let alone considered.

The Research Concept clearly fails to justify the use of animals that would be required to carry it out, and we call upon the Board of Scientific Counselors (BSC) to reject it decisively. Moreover, the fact that it results from nominations by an anonymous private citizen is unconscionable, and the BSC must demand transparency in the nomination process.

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N-Butylbenzenesulfonamide

Nomination of N-Butylbenzenesulfonamide (NBBS) by the National Institute of Environmental Health Sciences is based on concerns regarding possible widespread exposure from a number of different sources combined with indications from animal experiments of potential for neurotoxicity and reproductive toxicity and indications of potential for non-genotoxic carcinogenicity from Leadscope cell transformation models (NTP 2010).

In response, the NTP Research Concept (RC) proposes a comprehensive toxicological examination to occur in 3 phases: Phase 1 consists of in vitro assessment of endocrine activity and potential for neurotoxicity, toxicokinetics and ADME studies in rats and mice by both oral and i.p. exposure, an oral perinatal range-finding study in rats, and an oral 14-day repeat dose study in mice. Phase 2 includes an oral sub-chronic perinatal study in rats addressing reproduction, teratogenicity, neurotoxicity, and immunotoxicity plus an oral 90-day repeat dose study in mice. Phase 3 includes carcinogenicity studies in both rats and mice.

Specific Concerns

Non-genotoxic mechanisms of carcinogenicity should be explored in vitro before in vivo studies are considered: NBBS was evaluated in two sets of Leadscope carcinogenicity models; seven rodent models based on the 2-year rodent bioassays and four cell transformation assay models. NBBS was negative for carcinogenicity in all Leadscope rodent models. NBBS was positive in all Leadscope cell transformation models (NTP 2010). NBBS was not genotoxic in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, or TA1538 in the absence or presence of metabolic activation or in human lymphocytes. NBBS was negative in an in vitro Ames genotoxicity study. In a 2007 chromosomal aberration test with human lymphocytes (according to OECD TG 473) NBBS was found to be non-mutagenic in vitro (IUCLID).
NBBS does not appear to be genotoxic; however, there may be some concern regarding potential carcinogenicity via non-genotoxic mechanisms. Existing ToxCast information and other in vitro assessment of non-gentoxic mechanisms (e.g. cell proliferation, induction of receptor-mediated proliferation pathways) should be evaluated before any in vivo studies are considered. In addition, if the repeat dose studies proposed in Phase 1 or 2 are conducted, carcinogenicity assessments should be included (Cohen, 2010), in order to preclude the need for further carcinogenicity testing.

If NTP insists on additional animal testing, animal use for reproductive, developmental, neurotoxicity and immunotoxicity studies must be minimized: The RC does not describe the methods to be used to assess the various endpoints listed; however, the recommended study for Phase 2 is the Extended One Generation Reproductive Toxicity Study, a single study that assesses reproduction, teratogenesis, neurotoxicity and immunotoxicity following perinatal exposure (OECD, 2009). This combined study uses a total of 1400 animals, a large number but a savings over individual studies (Prenatal development, 1040 animals including pups; repro/developmental screen, 560; developmental neurotoxicity, 1200). We question the need for a second species for these studies as rat is the preferred and most well-developed model. Scientific justification should be made for replicating these studies in a second species.

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Selected Flame Retardants

NTP's research program for flame retardants, nominated by the by the Consumer Product Safety Commission (CPSC) in 2005, has reached its second phase, which is to include subchronic and chronic oral toxicity tests as well as neurotoxicity and/or developmental neurotoxicity tests on representative aromatic phosphates (APs). The representative APs identified initially for in-depth testing include triphenyl phosphate (TPP) and tert-butylphenyl diphenyl phosphate (BPDP).

TPP

TPP has been manufactured for more than 70 years with no indications of it causing any adverse health effects among production workers or users (EFRA, 2001). In particular, Sutton et al. (1960; cited in IPCS, 1991) found no evidence of neurological disease or other abnormalities in 32 workers exposed to TPP vapor, mist, or dust (at a time-weighted air concentration of 3.5 mg/m^3) for an average of 7.4 years.

As summarized in an Organisation for Economic Co-Operation and Development (OECD) Screening Information Data Sets (SIDS) Initial Assessment Report (SIAR; 2002), acute toxicity after oral and dermal administration in animals is very low. Acute oral administration in rats, mice, rabbits and guinea pigs produced LD50 values in a range of 3000 to above 20,000 mg/kg-bw – far above the typical limit dose applied in modern studies.

In addition, toxicity after repeated treatment of rats or rabbits with TPP is also low. Studies using dietary doses of up to 711 mg/kg-bw/day, or dermal doses of up to 1000 mg/kg-bw/day, evaluated clinical observations, body weight gain, food consumption, hematology, clinical chemistry, organ weights and histopathology. After 5 weeks of treatment, a slight depression of body weight gain and an increase of liver weights were observed at a dietary dose level of 350 mg/kg-bw/day in rats while 70 mg/kg bw/day in the diet produced no effect. Four month studies at dietary doses of up to 711 mg/kg-bw/day confirmed these effects on body and liver weight, with no effects on general well being, immune and nervous systems reported. The low toxicity was confirmed after dermal exposure of 100 and 1000 mg/kg bw/day in rabbits for 15 days with depression of acetylcholinesterase reported to be the only dose related effect.

In studies of reproductive and developmental toxicity in Sprague-Dawley rats, Welsh et al. (1987; cited in IPCS, 1991) fed TPP corresponding to daily intakes of 0, 166, 341, 516, and 690 mg/kg-bw from 4 weeks post weaning for 91 days, through mating and gestation. TPP exposure had no toxic effects on mothers or offspring at these dosages. No significant increase in the incidence of developmental anomalies was seen in treated animals as compared to values in control animals and the types of anomalies were similar in both treated and control groups. The authors concluded that TPP was not teratogenic in Sprague-Dawley rats at the levels tested.

Despite an early report to the contrary, TPP is not considered neurotoxic in animals or humans. Smith et al. (1930, 1932; cited in IPCS, 1991) reported delayed neuropathy in cats and monkeys exposed to TPP. However, Wills et al. (1979; cited in IPCS, 1991) was unable to reproduce this effect and reported that 99.9%-pure TPP did not produce any evidence of axonal degeneration, demyelination, or any other pathological changes at 11 levels of the nervous system (from the cerebral cortex to peripheral nerves) when subcutaneously injected into cats at doses of 0.4, 0.7, or 1.0 g/kg. Since neurotoxicity is a potential adverse effect of many organophosphates, Wills et al. (1979) suggested that at the high doses of TPP used by Smith et al. (1930, 1932), even small concentrations of impurities might have sufficient activity to produce axonal degeneration and demyelination. Subsequently, Sobotka et al. (1986; cited in IPCS, 1991) fed male Sprague-

Dawley rats diets containing TPP at levels of 0, 2.5, 5, 7.5, or 10 g/kg for 4 months and found no evidence of neuromotor toxicity.

Tests for gene mutations in bacteria as well as yeast and mammalian cells did not reveal any sign of mutagenicity. An UDS-test in syrian hamster fibroblast cells showed no genotoxic effect (SIAR, 2002).

Although no long term carcinogenicity assays were found, there is relevant data from a study using male strain A/St mice. These mice, who show a very high sensitivity to carcinogens as manifested by short latency periods and high tumor rates, were treated by intraperitoneal injection with 20, 40 or 80 mg/kg-bw (single dose) TPP 3 times per week and observed for 18 weeks. Afterwards, lungs were examined for adenomas, which were observed only in the 80 mg/kg bw group with no significant increase of incidence (Theiss et al., 1977; cited in SIAR, 2002).

The International Programme on Chemical Safety (INCHEM) concluded in 1991 that the available data on TPP indicate no hazard to humans. Likewise, in its SIAR (2002), OECD concluded that for human health effects, TPP is currently of low priority for further work.

BPDP

While the Research Concept notes that studies on commercial AP products which may contain multiple isomeric forms or be formulated together with other flame retardants are difficult to interpret with respect to the toxicity of discrete AP components, we urge NTP to fully consider the relevance of all existing data prior to initiating duplicative studies that are unlikely to produce any new information that would be useful or relevant.

In its 2006 comments, the Phosphate Ester Flame Retardant Consortium (Pefrc) noted that BPDP along with the other aromatic phosphates are represented by manufactures in international initiatives reviewing and summarizing existing data as well as identifying and addressing and data gaps. Akzo Nobel Functional Chemicals submitted a High Production Volume (HPV) Chemicals Challenge Program test plan and robust summaries to the US Environmental Protection Agency (EPA) for butylated triphenyl phosphate in 2004 with CAS No. 220352-35-2 replacing CAS no. 68937-40-6. (Pefrc identifies CAS No. 56803-37-3 as both tert-butylphenyl diphenyl phosphate and tertbutylated triphenyl phosphate with the additional CAS no. 68937-40-6.) In subsequent communications with EPA, Azko Nobel states that in essentially all of the referenced studies, the test substance, consisting of a commercial product sold under several product names, is a mixture of tert-butylated triphenyl phosphate isomers. In 2003, Azko Nobel tested one of these substances, Phosflex 61B, in a Guideline OECD 421 Reproductive/Developmental Toxicity Study on rats. Since this recent GLP study directly addresses endpoints of concern in the research concept its summary is presented in its entirety from the company's HPV Program submission.

> Twelve male and 12 female rats received Phosflex 61B by oral gavage daily for 2 weeks prior to mating, during the 2 week mating period, and through gestation and lactation. Doses administered were either 0 (vehicle control), 50,250, or 1000 mg/kg/day. End points measured during the study include parental food consumption, body weight, body weight gain, reproductive performance, organ weights, and histopathology of the reproductive organs. Also evaluated were offspring body weights and survival, litter size, and the presence of gross anomalies. The daily administration of Phosflex 61B to male and female rats did not result in clinical signs of toxicity, or in changes in food consumption, body weights, body weight gain, or in organ weights. There were no

treatment-related histological changes in the reproductive organs. Further, there were no significant differences in litter size or the number of live pups on postnatal days 0 and 4. The NOAEL for reproductive toxicity is 1000 mg/kglday. The NOAEL for reproductive toxicity is greater than 1000 mg/kg/day.

Three acute delayed neurotoxicity tests presented in the same HPV program submission also produced completely negative results. Two used Phosplex 51B (Supresta, formerly Azko Nobel, 1980) and one Durad 220B (Chemtura, 1992). Each of these studies effectively used tri-ortho-cresyl phosphate (TOCP) as a positive control.

Conclusion

While we commend NTP's proposed use of *in vitro* studies to screen the APs for mechanism of action and relative potency, we question the choice of TPP and BPDP for initial in-depth animal testing. TPP has a long history of safe use and has been found to present a low concern for human health effects by both INCHEM (1991) and OECD (2002). BPDP is represented by manufacturers in international chemical risk assessment initiatives and a commercial product consisting of tert-butylated triphenyl phosphate isomers was the subject of a 2003 GLP study addressing reproductive and developmental toxicity endpoints in rats. We urge the Board of Scientific Counselors to consider this existing data and human experience and reject any proposals for new animal tests for TPP and BPDP.

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